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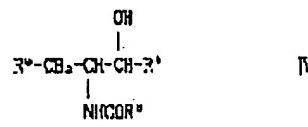
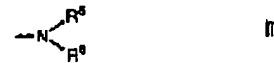
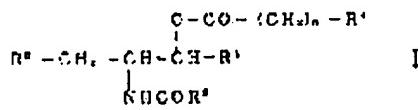
FUJIWARA MICHIIRO

(54) AMINOALCOHOL DERIVATIVE AND PHARMACEUTICAL CONTAINING THE SAME

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a novel aminoalcohol derivative that has excellent therapeutic effect on neurological disorder and brain-protecting action and is useful as a therapeutic agent for neurological disorder, particularly as a brain-protecting agent.

SOLUTION: This novel compound is an aminoalcohol derivative represented by formula I [R1 is an alkyl, an alkenyl, a cycloalkyl, an aryl; R2 is an alkyl, a hydroxyalkyl, an alkenyl, a hydroxyalkenyl; R3 is a group of formula II, formula III (R5 and R6 are each H, an alkyl, piperidino); R4 is H, an alkyl, an amino, an alkoxy, carboxyl; n is 1-4] or its pharmaceutically acceptable salt, typically (1S, 2S)-2-decanoylamino-3-morpholino-1-phenyl-1-propyl acetate. The compound of formula I is prepared, for example, by esterification of the hydroxyl group in the compound of formula IV with a carboxylic acid or its reactive derivative corresponding to CO-(CH₂)_n-R4.



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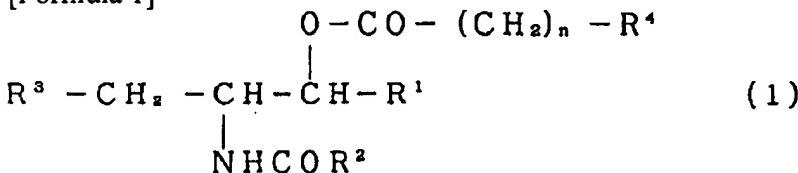
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CLAIMS

[Claim(s)]

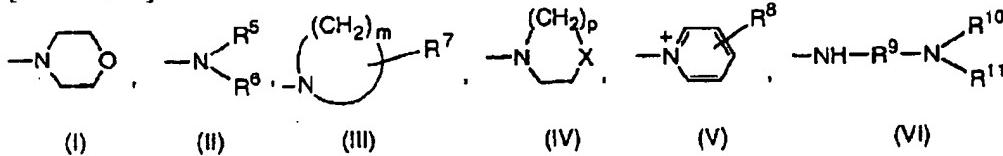
[Claim 1] The amino alcohol derivative shown by the following formula (1), or its salt permitted pharmacologically.

[Formula 1]



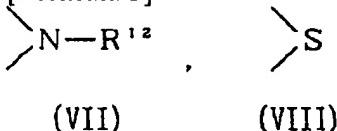
R1 shows among [type the aryl group which may have the cycloalkyl radical or substituent which may have the alkyl group, the alkenyl radical, and the substituent. R2 An alkyl group, a hydroxyalkyl radical, an alkenyl radical, a hydroxy alkenyl radical, An alkoxyl group or an aralkyloxy radical is shown and it is R3. The following formula (I) The permutation amino group expressed with - (VI) is shown. R4 It is] a hydrogen atom, a low-grade alkyl group, the amino group, monochrome or a JI low-grade alkylamino radical, a low-grade alkoxyl group, or a carboxyl group is indicated to be, and n indicates the integer of 1-4 to be.

[Formula 2]



That R5 and R6 are the same or the difference among [type, a hydrogen atom, a low-grade alkyl group, A low-grade alkenyl radical, a hydroxy low-grade alkyl group, a low-grade alkoxyalkyl group, the piperazino radical by which an amino low-grade alkyl group, the cycloalkyl radical, the hydroxy cycloalkyl radical, the aralkyl radical, or the low-grade alkyl group may be permuted -- expressing -- R7 And R8 The same or a difference, a hydrogen atom, hydroxyl, a low-grade alkyl group, a low-grade alkoxy group, A hydroxy low-grade alkyl group, a carboxyl group, a low-grade alkoxy carbonyl group, The radical chosen from an aralkyl radical, a piperidino radical, an acyloxy radical, the amino group, and an amino low-grade alkyl group is expressed. R9 The low-grade alkylene group which may be interrupted for oxygen is expressed. R10 and R11 Express the same or a difference, a hydrogen atom, a low-grade alkyl group, or a hydroxy low-grade alkyl group, or R10 and R11 [or] the piperidino radical or morpholino radical which the low-grade alkyl group may permute with the nitrogen atom which they have combined -- expressing -- m -- the integer of 2-6 -- expressing -- p -- 2 or 3 -- expressing -- X -- the following type (VII) -- or (VIII) it expresses.

[Formula 3]



(R12 expresses a low-grade alkyl group, an acyl group, a low-grade alkoxy carbonyl group, or a pyridyl radical among a formula)]

[Claim 2] It sets to a general formula (1) and is R1. It is the phenyl group which may have the substituent. R2 The alkyl group, alkoxy group, or aralkyloxy radical of carbon numbers 2-19 is shown. R3 morpholino radical; -- low-grade alkylamino radical; -- morpholino low-grade alkylamino radical; even if it permutes by the pyrrolidino radical; low-grade alkyl which may be permuted by the cycloalkylamino radical; hydroxyl or hydroxy low-grade alkyl which may be permuted by the hydroxyl A good piperazino radical; the amino alcohol derivative according to claim 1 which is the permutation amino group chosen from the piperidino radical which may be permuted by screw (hydroxy low-grade alkyl) amino-group; and the hydroxyl, or hydroxy low-grade alkyl.

[Claim 3] It sets to a general formula (1) and is R1. It is a phenyl group and is R2. It is a nonyl radical, an octyloxy radical, or a benzyloxy radical, and is R3. It is a morpholino radical, a cyclohexylamino radical, a cyclopentylamino radical, a pyrrolidino radical, N-methyl piperazino radical, the JIETA Norian amino group, a hydroxy piperidino radical, or a piperidino radical, and is R4. Amino alcohol derivative according to claim 1 which is a hydrogen atom, a dimethylamino radical, a methoxy group, or a carboxyl group.

[Claim 4] It sets to a general formula (1) and is R1. It is a phenyl group and is R2. It is a nonyl radical, an octyloxy radical, or a benzyloxy radical, and is R3. It is a morpholino radical, N-methyl piperazino radical, or a JIETA Norian amino group, and is R4. Amino alcohol derivative according to claim 1 the configuration of whose it is a hydrogen atom, a dimethylamino radical, a methoxy group, or a carboxyl group, and is (1S, 2S).

[Claim 5] a general formula (1) -- setting -- R1 a phenyl group -- it is -- R2 a nonyl radical, an octyloxy radical, or a benzyloxy radical -- it is -- R3 a hydroxy piperidino radical -- it is -- R4 a hydrogen atom, a dimethylamino radical, a methoxy group, or a carboxyl group -- it is -- the configuration -- (1S, 2S) -- or (1R, 2S) (1S, 2R) -- it is -- amino alcohol derivative according to claim 1.

[Claim 6] It sets to a general formula (1) and is R1. It is a phenyl group and is R2. It is a nonyl radical, an octyloxy radical, or a benzyloxy radical, and is R3. It is a morpholino radical, a pyrrolidino radical, a piperidino radical, a cyclohexylamino radical, or a cyclopentylamino radical, and is R4. Amino alcohol derivative according to claim 1 the configuration of whose it is a hydrogen atom, a dimethylamino radical, a methoxy group, or a carboxyl group, and is (1R, 2R).

[Claim 7] Physic which contains the amino alcohol derivative of claim 1-6 given in any 1 term, or its salt permitted pharmacologically as an active principle.

[Claim 8] Physic according to claim 7 which is the therapy agent of a nervous disease.

[Claim 9] Physic according to claim 8 which is the therapy agent of the nervous disease which contains an amino alcohol derivative or its salt permitted pharmacologically according to claim 4 or 5 as an active principle.

[Claim 10] Physic according to claim 8 or 9 whose therapy agent of a nervous disease is a brain protective agent.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to the physic containing the amino alcohol derivative and it which are a ceramide analog, especially the therapy agent of a nervous disease.

[0002]

[Description of the Prior Art] Sphingoglycolipid (henceforth GSL) exists as a cell membrane surface constituent of a mammalian cell, and it is known that it is closely related to cell functions, such as generating through the receptor function of a physiological active substance, the mutual recognizing ability between cells, or biotaxis, growth, differentiation, canceration, and an immunoreaction.

[0003] Especially, ganglioside is GSL containing a sialic acid and the effectiveness of the exogenous ganglioside to the various symptoms models of a nervous system is examined by recovery of nervous diseases, such as peripheral nerve injury and a central-nerves failure, i.e., the flume crack which has activity in the nervous promotion of playback and a nervous neural transmission process, and current. It is already KURONA sial (CronassialTM) in Italy as drugs using this. Kamiichi of the drugs is carried out and related patent application is made (JP,52-34912,A).

[0004] Although current and the thing currently that as the technique of exploring the function of ganglioside used are things of the type of adding ganglioside from outside in an experiment system, relation with endogenous ganglioside poses a problem in that case. [most] That is, it is thought that the result from which the endogenous ganglioside which exists in a cell membrane adds ganglioside further in [which have already formed complex] various cell surface receptors etc., and is drawn in is not always reflecting a true cell physiology-meaning of endogenous ganglioside. therefore -- in order to know the original role on the cell physiology of ganglioside -- endogenous -- the method of changing the biosynthesis of GSL specifically was required. this invention person etc. is 1-phenyl-2-decanoylamino-3-morpholino-1-propanol which is the analog of ceramide previously. (PDMP) It compounds. all the cells of GSL to which D-threo-PDMP checks a glucoseylceramide biosynthesis enzyme specifically, and uses a glucoseylceramide as starting material -- entailment -- it proved decreasing an amount remarkably (J.Lipid.Res., vol.28, 565-571, 1987).

[0005] Furthermore, a GSL content falls by D-threo-PDMP and it is reported that expansion of a neural spine is controlled by this (103 J. Biochem., 110, 96- 1991). Moreover, D-threo-PDMP controls a synapse function and it is found out that this control is specifically canceled by GQ1b in various gangliosides (Biochem.Biophys.Res.Commun., 222, 494-498, 1996). From this result, the importance which it is suggested that ganglioside GQ1b is an activated molecule indispensable to a synapse function, and it exerts on the neurological function of endogenous ganglioside is recognized.

[0006] this invention persons have found out that L-threo-PDMP which is the optical antipode of D-threo-PDMP may promote the biosynthesis of GSL on the other hand (J.Cell.Physiol., 141, 573-583 (1989)). However, [whether L-threo-PDMP makes the endogenous ganglioside level of a nerve cell increase, and whether the increment in endogenous ganglioside activates the function of a nerve cell again], it is a strange problem and examination was not made at all.

[0007] Then, by promoting the ganglioside biosynthesis of a nerve cell, 2-acylamino propanol derivatives, such as L-threo-PDMP, demonstrated the neural spine expansion facilitatory effect (J.Neurochem., 67, 1821-1830 (1996)) and the synaptogenesis facilitatory effect, and, as for this invention persons, have found out that it is promising as a neurotropia agent (PCT international public presentation WO 95/05177).

[0008] The recently and this invention persons are MAP activated when synaptic transmission is continuously risen

by N-methyl-D-aspartate (NMDA), a brain-derived neurotrophic factor (Brain Derived Neurotrophic Factor; BDNF), etc. for the purpose of the elucidation of the action mechanism of the neurotrophic factor Mr. activity of L-threo-PDMP. The effect of this matter to a kinase (MAPkinase; mitogen-activated protein kinase) was considered. Consequently, L-threo-PDMP is proportional to a synaptogenesis facilitatory effect, and MAP. It has become clear that long duration activation of the kinase is carried out. Furthermore, the activation effectiveness of the GQ1b synthetic enzyme activity by L-threo-PDMP is also found out.

[0009] However, above L-threo-PDMP is in vivo. When demonstrating drug effect, it was judged that there was room of amelioration further about the half-life in blood and brain internal transmigration nature.

[0010]

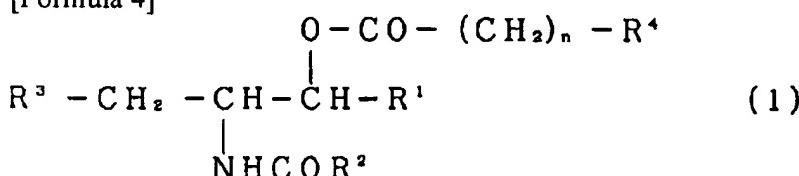
[Problem(s) to be Solved by the Invention] this invention persons found out that solubility was improved remarkably by esterifying the hydroxyl group of 2-acylamino propanol derivatives, such as L-threo-PDMP. Moreover, when mammalian was medicated with esterified L-threo-PDMP, it checked having the neuroprotection effectiveness and the brain protective action superior to L-threo-PDMP. Based on these knowledge, it came to complete this invention.

[0011]

[Means for Solving the Problem] This invention is [1] general formula (1).

[0012]

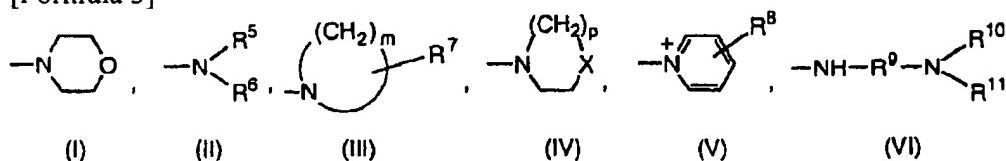
[Formula 4]



[0013] The inside of [type, the cycloalkyl radical on which R1 may have the alkyl group, the alkenyl radical, and the substituent, Or the aryl group which may have the substituent is shown and it is R2. Alkyl group, A hydroxyalkyl radical, an alkenyl radical, a hydroxy alkenyl radical, an alkoxy group, or an aralkyloxy radical is shown. R3 The following type (I) The permutation amino group expressed with - (VI) is shown, and it is R4. It is] a hydrogen atom, a low-grade alkyl group, the amino group, monochromic or a π low-grade alkylamino radical, a low-grade alkoxy group, or a carboxyl group is indicated to be, and n indicates the integer of 1-4 to be.

[0014]

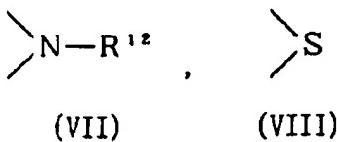
[Formula 5]



[0015] That R5 and R6 are the same or the difference among [type, a hydrogen atom, a low-grade alkyl group, A low-grade alkenyl radical, a hydroxy low-grade alkyl group, a low-grade alkoxyalkyl group, An amino low-grade alkyl group, a cycloalkyl radical, a hydroxy cycloalkyl radical, The piperazino radical by which an aralkyl radical or low-grade alkyl may be permuted is expressed. R7 And R8 The same or a difference, a hydrogen atom, hydroxyl, a low-grade alkyl group, A low-grade alkoxy group and hydroxy low-grade alkyl group, a carboxyl group, A low-grade alkoxy carbonyl group, an aralkyl radical, a piperidino radical, an acyloxy radical, The radical chosen from the amino group and an amino low-grade alkyl group is expressed, and it is R9. The low-grade alkylene group which may be interrupted for oxygen is expressed. R10 and R11 Express the same or a difference, a hydrogen atom, a low-grade alkyl group, or a hydroxy low-grade alkyl group, or R10 and R11 [or] the piperidino radical or morpholino radical which low-grade alkyl may permute with the nitrogen atom which they have combined -- expressing -- m -- the integer of 2-6 -- expressing -- p -- 2 or 3 -- expressing -- X -- the following type (VII) -- or (VIII) it expresses.

[0016]

[Formula 6]



permutation = substituent

[0017] (R12 expresses a low-grade alkyl group, an acyl group, a low-grade alkoxy carbonyl group, or a pyridyl radical among a formula) It is related with the amino alcohol derivative shown by], and its salt permitted pharmacologically.

[0018] Moreover, it sets to [2] general formulas (1), and this invention is R1. It is the phenyl group which may have the substituent. R2 The alkyl group, alkoxy group, or aralkyloxy radical of carbon numbers 2-19 is shown. R3 ** morpholino radical; -- low-grade alkylamino radical; -- morpholino low-grade alkylamino radical; even if it permutes by the pyrrolidino radical; low-grade alkyl which may be permuted by the cycloalkylamino radical; hydroxyl or hydroxy low-grade alkyl which may be permuted by the hydroxyl A good piperazino radical; it is the permutation amino group chosen from the piperidino radical which may be permuted by screw (hydroxy low-grade alkyl) amino-group; and the hydroxyl, or hydroxy low-grade alkyl, and is R4. Amino alcohol derivative which is as being the above;

[3] Set to a general formula (1) and it is R1. It is a phenyl group and is R2. It is a nonyl radical, an octyloxy radical, or a benzyloxy radical, and is R3. It is a morpholino radical, a cyclohexylamino radical, a cyclopentylamino radical, a pyrrolidino radical, N-methyl piperazino radical, the JIETA Norian amino group, a hydroxy piperidino radical, or a piperidino radical, and is R4. Amino alcohol derivative which is a hydrogen atom, a dimethylamino radical, a methoxy group, or a carboxyl group;

[4] Set to a general formula (1) and it is R1. It is a phenyl group and is R2. It is a nonyl radical, an octyloxy radical, or a benzyloxy radical, and is R3. It is a morpholino radical, N-methyl piperazino radical, or a JIETA Norian amino group, and is R4. Amino alcohol derivative the configuration of whose it is a hydrogen atom, a dimethylamino radical, a methoxy group, or a carboxyl group, and is (1S, 2S);

[5] a general formula (1) -- setting -- R1 a phenyl group -- it is -- R2 a nonyl radical, an octyloxy radical, or a benzyloxy radical -- it is -- R3 a hydroxy piperidino radical -- it is -- R4 a hydrogen atom, a dimethylamino radical, a methoxy group, or a carboxyl group -- it is -- the configuration -- (1S, 2S) -- or (1R, 2S) (1S, 2R) -- it is -- amino alcohol derivative;

[6] Set to a general formula (1) and it is R1. It is a phenyl group and is R2. It is a nonyl radical, an octyloxy radical, or a benzyloxy radical, and is R3. It is a morpholino radical, a pyrrolidino radical, a piperidino radical, a cyclohexylamino radical, or a cyclopentylamino radical, and is R4. It is a hydrogen atom, a dimethylamino radical, a methoxy group, or a carboxyl group, and is related with amino alcohol derivative; the configuration of whose is (1R, 2R). Furthermore, this invention relates to the therapy agent or brain protective agent of a nervous disease especially about the physic containing the amino alcohol derivative expressed with the above-mentioned general formula (1), or its salt permitted pharmacologically. the configuration of the compound of the general formula (1) in above-mentioned [4]- [6], (1S, 2S), and (1R, 2S) -- or (1S, 2R) (1R, 2R) it is equivalent to L-threo object, L-erythro object, D-erythro object, or D-threo object, respectively. [in addition,]

[0019] Hereafter, this invention is explained concretely.

[0020] In this invention, it means that carbon numbers are 1-6 as it is low-grade.

[0021] The inside of the above-mentioned formula, and R1 As for the carbon number of the radical to express, 6-15 are desirable, and the low-grade alkyl and low-grade alkoxy ** hydroxyl, hydroxy low-grade alkyl, or the nitro group of a substituent is desirable. The phenyl group which may be permuted by 1-3 substituents preferably chosen from the low-grade alkyl and low-grade alkoxy ** hydroxyl, hydroxy low-grade alkyl, and nitroglycerine as an aryl group which may have the substituent, for example, a phenyl group, a dimethoxy phenyl group, and a dihydroxy phenyl group are mentioned, and a phenyl group is mentioned still more preferably. Moreover, a cyclohexyl radical is mentioned as a cycloalkyl radical.

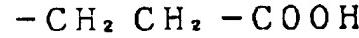
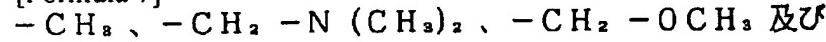
[0022] The inside of a formula, and R2 As for the carbon number of the radical to express, 2-19 are desirable, and they are the alkyl groups (for example, passing PUCHIRU, nonyl, undecyl, tridecyl, pentadecyl, etc.) of carbon numbers 7-15 or a hydroxyalkyl radical (they are PUCHIRU, hydroxy nonyl, hydroxy undecyl, hydroxy tridecyl, hydroxy pentadecyl, etc. to HIDOROKISHI), the alkoxy group (for example, t-butoxy, n-octyloxy) of carbon numbers 4-14, or an aralkyloxy radical (for example, benzyloxy) more preferably. R2 The most desirable example is a nonyl radical, n-octyloxy radical, or a benzyloxy radical.

[0023] the inside of a formula, and R3 desirable -- morpholino radical; -- low-grade -- alkylamino radical;

morpholino -- low-grade -- the piperidino radical which may be permuted by the piperazino radical; screw (hydroxy low-grade alkyl) amino-group; hydroxyl or hydroxy low-grade alkyl which may be permuted by the pyrrolidino radical; low-grade alkyl which may be permuted by the cycloalkylamino radical; hydroxyl or hydroxy low-grade alkyl which may be permuted by the alkylamino radical; hydroxyl is mentioned. A morpholino radical, a cyclohexylamino radical, a cyclopentylamino radical, a pyrrolidino radical, N-methyl piperazino radical, the JIETA Norian amino group, a hydroxy piperidino radical, or a piperidino radical is mentioned more preferably. the most desirable radical -- the purpose of using the amino alcohol derivative of this invention, and an asymmetric carbon atom -- it changes with configurations to kick. R3 R3 when it is a morpholino radical, N-methyl piperazino radical, or a JIETA Norian amino group and configurations are (1S, 2S) a hydroxy piperidino radical -- it is -- a configuration -- (1S, 2S) -- or (1R, 2S) (1S, 2R) -- it is -- a case -- a glycolipid biosynthesis promotion operation and neural spine expanding activity -- strong -- a nervous disease -- it is useful especially as a therapy agent. On the other hand, it is R3. It is a morpholino radical, a pyrrolidino radical, a piperidino radical, a cyclohexylamino radical, or a cyclopentylamino radical, and when configurations are (1R, 2R), glycolipid biosynthesis depressant action or a differentiation-inducing operation is strong, and useful as a cancer treatment agent.

[0024] The inside of a formula, and R4 As a low-grade alkyl group to express, the alkyl groups (methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, etc.) of carbon numbers 1-4 are desirable. As monochrome or a JI low-grade alkylamino radical, the amino groups (methylamino, ethylamino, propylamino, butylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, etc.) which have 1 or said two low-grade alkyls are desirable. As a low-grade alkoxy group, the alkoxy groups (methoxy and ethoxy ** propoxy, isopropoxy, butoxy one, iso butoxy, s-butoxy, t-butoxy, etc.) of carbon numbers 1-4 are desirable. Although n is the integer of 1-4, it is 1 or 2 preferably. R4 Carrying out, a more desirable radical is a hydrogen atom, a dimethylamino radical, a methoxy group, or a carboxyl group, and is a hydrogen atom most preferably. - CH₂n-R4 As a desirable example, it is [0025].

[Formula 7]



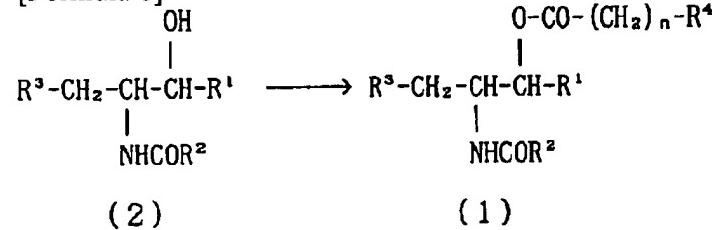
[0026] *****

[0027] The amino alcohol derivative of this invention shown by the formula (1) is the hydroxyl group of the amino alcohol derivative shown by the formula (2) $\text{CO}-(\text{CH}_2)_n-\text{R}_4$. Although obtained by the esterification reaction which is the approach of the very thing known using a corresponding carboxylic acid or its reactant derivative, it is not limited to such an approach.

[0028] R1 of the amino alcohol derivative shown by the formula (2), and R2 Or R3 Deprotection may be carried out, after protecting this functional group by the suitable protective group beforehand and performing an esterification reaction, when a reactant functional group is contained to an esterification reagent.

[0029]

[Formula 8]



[0030] The approach using the above-mentioned carboxylic acid and a condensing agent as the esterification approach, the approach using an acid anhydride, the approach using acid halide, etc. are illustrated. The amino alcohol derivative shown by the formula (2), or its acid addition salt (for example, hydrochloride) specifically A methylene chloride, the inside of organic solvents, such as a pyridine, the above-mentioned carboxylic acid, a condensing agent (for example, dicyclohexylcarbodiimide (DCC)), and an esterification catalyst (for example, N and N-dimethylamino pyridine --) the approach, the acid anhydride or acid halide (for example, acid chloride) made to react using N-pyrrolidino pyridine, and a base (for example, a pyridine --) The approach of making it react using organic bases, such as triethylamine, diisopropyl ethylamine, and N-methyl morpholine, and an inorganic base like

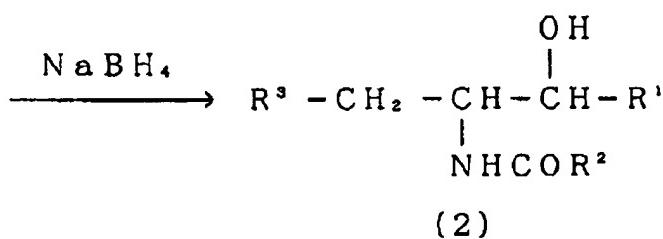
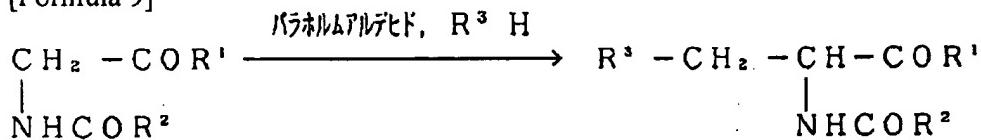
a sodium hydrogencarbonate etc. is illustrated. In addition, if the above-mentioned organic solvent does not check an esterification reaction but the above-mentioned amino alcohol derivative is dissolved, it is not limited especially, and if the above-mentioned esterification catalyst also promotes an esterification reaction, it will not be limited especially.

[0031] an esterification reaction -- usually -- about 0-50 degrees C -- preferably, for the bottom of a room temperature (5-35 degrees C (JIS K0050)), and several hours - several days, although preferably carried out for 10 hours - two days, if a reaction condition is this contractor, it can be suitably set up by preliminary experiment. this invention compound expressed with a formula (1) can be refined and isolated after an esterification reaction, combining suitably the solvent extraction by ethyl acetate, chloroform, etc., various chromatographies (adsorption chromatography, ion exchange chromatography, etc.), and the purification means of the very thing known of crystallization.

[0032] The compound expressed with the above-mentioned formula (2) is compounded according to the following approach indicated by for example, J.Lipid.Res., Vol.28, 565-571 (1987) and J.Biochem., Vol.111, and 191-196 (1992), and is obtained by carrying out optical resolution if needed.

[0033]

[Formula 9]

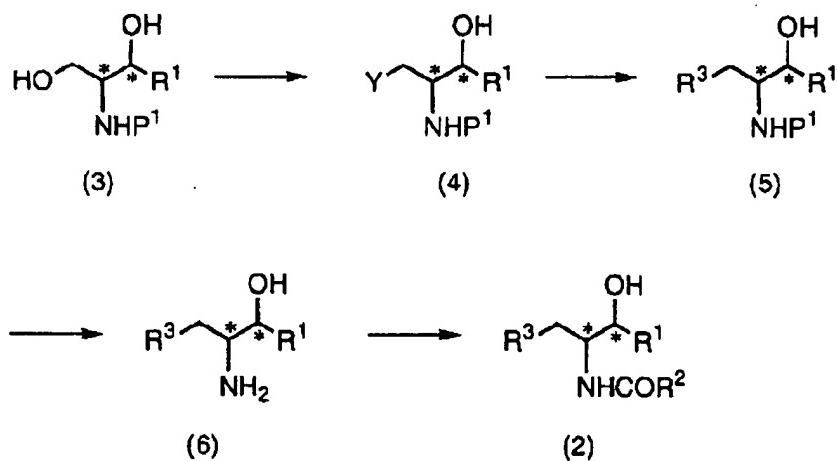


[0034] That is, it sets to the compound expressed with a formula (2), for example, and is R1. When R2 CO is an acyl group, after carrying out condensation of the 2-acylamino acetophenone to secondary amine (R3 H) by the Mannich reaction by the phenyl group, it returns with a sodium borohydride. Mixture of four isomers obtained by this is fractional-crystallization-ized with chloroform/ether (diastereomer division). After acquiring D, L-threo object and D, and L-erythro object as racemic modification, respectively, further again by fractional-crystallization-izing this racemic modification with a salt [optical activity / acid / a tartaric acid, a dibenzoyl tartaric acid, / camphor] (optical resolution) The compound which has a desired configuration can be obtained as an optical activity salt. Furthermore, by the approach of this contractor performing easily, a salt can be removed and the purpose compound can be obtained as a basic compound of isolation.

[0035] Moreover, the compound expressed with the above-mentioned formula (2) is obtained as a compound which uses the chiral compound expressed with a formula (3) as starting material, and has a desired configuration by carrying out a sequential reaction, as shown below.

[0036]

[Formula 10]



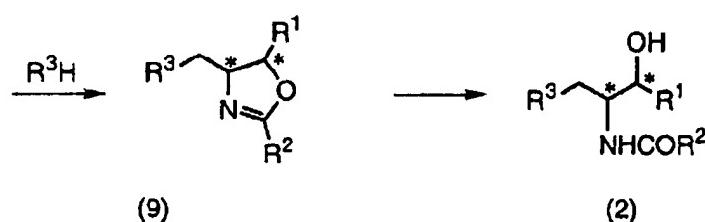
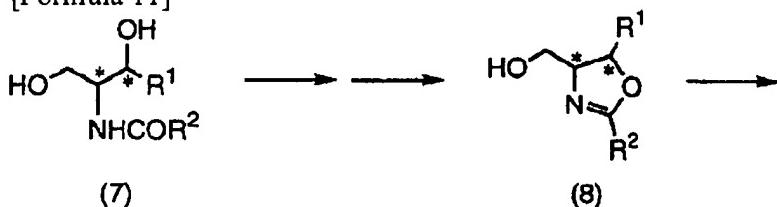
[0037] [Among a formula, * expresses asymmetrical carbon; P1 is the protective group of the amino group, for example, a benzylloxycarbonyl radical, a t-butoxycarbonyl group, a benzenesulphonyl radical, a fluorenyl methoxy carbonyl group, etc. are mentioned, and; Y expresses leaving groups, such as a methane sulfonyl, a trihalogeno methane sulfonyl, P-tosyl, benzenesulphonyl, and P-bromobenzene sulfonyl group.]

[0038] Namely, after considering as the compound which introduces a leaving group (Y) only into the 1st class hydroxyl group of the amino alcohol derivative shown by the formula (3), and is shown by the formula (4), Make the amine shown in this compound by formula R³H react, and it considers as the amino alcohol derivative shown by the formula (5). It is P1 from this compound. The chiral amino alcohol derivative shown by the formula (2) can be obtained by considering as the amino alcohol derivative which is desorbed and is shown by the formula (6), and making the carboxylic acid subsequently shown by R²COOH, or its reactant derivative react.

[0039] Moreover, the compound shown by the above-mentioned formula (2) is obtained as a compound which has a desired configuration by following the synthetic path which makes the compound (8) which has an oxazoline ring synthetic intermediate field by using a chiral compound (7) as starting material, as shown below.

[0040]

[Formula 11]



[0041] That is, after introducing a leaving group into the 1st class hydroxyl group again, making it react with an amine (R³H), after considering as the compound (8) which is made to carry out the ring closure of the leaving group (Y) only to the 1st class hydroxyl group of a compound (7) under basic conditions after installation, and has an oxazoline ring, and considering as a compound (9), a chiral amino alcohol derivative (2) can be obtained by carrying out ring breakage of the oxazoline ring by acid treatment. As a salt of the compound shown by the formula (1) permitted pharmacologically, the salt of organic acids, such as inorganic-acid salts, such as a hydrochloric acid, a phosphoric acid, a sulfuric acid, and a nitric acid, a formic acid, an acetic acid, a citric acid, a lactic acid, a malic acid, oxalic acid, a maleic acid, a fumaric acid, a succinic acid, trifluoroacetic acid, methansulfonic acid (mesyl acid), and P-toluenesulfonic acid, can be mentioned. What is necessary is to dissolve the compound (isolation

mold) which can perform manufacture of such a salt by the approach of the very thing known, for example, is shown by the formula (1) in proper solvents, such as alcohol, to add, to make the above-mentioned acid about equimolar usually react, and just to distill out a solvent by request.

[0042] [Solubility] Rather than the case where it is an isolation mold, solubility [as opposed to water or a physiological saline in the direction in the case of being salt types, such as a hydrochloride, citrate, a lactate, and succinate] of this invention compound improves. For example, the solubility to the physiological saline of an L-threo-PDMP hydrochloride is 0.5mg/ml. For the hydrochloride (example 1-2) of the compound of the example 1 which carried out acetyl esterification of the L-threo-PDMP, solubility [as opposed to / solubility is improved very much and / a physiological saline and 1% Tween 80 (Tween80) content physiological saline] is 100mg/ml to being extent, respectively. It was above. Moreover, solubility [as opposed to / solubility of citrate (example 1-2) of the compound of an example 1-1 improves very much, and / a physiological saline and 1% Tween 80 content physiological saline] is 100mg/ml. It was above.

[0043] [Operation] this invention compound has the operation which controls the biosynthesis of a glycolipid, and has the usefulness as physic based on this operation. As for the compound shown by the formula (1), the above-mentioned biosynthesis control action changes with the configuration (L-threo, L-erythro, D-threo, D-erythro). Among these, the compound which has a glycolipids (ganglioside etc.) biosynthesis promotion operation has a neural spine expansion facilitatory effect, a synaptogenesis facilitatory effect, the nerve cell death prevention effectiveness, and the MAP kinase activation effectiveness, and is in vivo. Since it sets and has the memory disorder improvement effect and the brain protective effect over a potassium-cyanide inducement hypoxia model animal, it is useful as a neuriatria agent based on such effectiveness. Therefore, this animal can be treated by medicating mammalian including the Homo sapiens suffered from the nervous disease resulting from the failure of a peripheral nerve or the central nerves in the effective dose of this invention compound. The various central nervous system diseases it is expected as a typical disease by reproducing nerve fibers, such as cerebral apoplexy, cerebral infarction, a cerebrovascular-disease sequela, the cerebral hemorrhage, brain injury, a memory disorder, senile dementia, an Alzheimer disease, and a Parkinson Mr. disease, that curative effects are; various peripheral nervous system diseases, such as cacochemia nature polyneuropathy [for example,], mechanical neuropathy, and toxicity neuropathy, are mentioned to a list. Although this invention compound especially whose configuration is L-threo has the strong operation as a neuriatria agent, as long as it has a glycolipid biosynthesis promotion operation, it is not limited to a configuration, for example, the compound of configurations other than L-threo object can also be used not only for a compound given in the above [4] which is L-threo object but for the above [5] as an active principle of a neuriatria agent like the compound of a publication. Moreover, the effectiveness that the above this invention compounds prevent the nerve cell death of hippocampus CA1 field is accepted. It compares with the parent compound (the part of -O-CO-(CH₂) n-R₄ in a formula (1) - compound which is OH) of this invention compound. Moreover, since brain internal transmigration nature is high and the disappearance out of a brain also has it, [slow] It is effective in the therapy of for example, a cerebrovascular-disease sequela as a central nervous system disease therapy agent especially a brain protective agent, or cranial nerve activation and a protective agent.

[0044] The compound which, on the other hand, has glycolipid composition inhibitory action among this invention compounds has the operation which normalizes the operation or cancer cell which guides the differentiation of a cell which carries out a plague in the undifferentiated condition, and is useful as a cancer treatment agent. this invention compound whose configuration is D-threo or L-threo is preferably used for such an application, and especially its D-threo object is desirable. For example, a compound given in the above [6] can be used for such a purpose.

[0045] [Pharmaceutical-preparation-izing] this invention compound can be considered as taking orally or the pharmaceutical preparation parenterally prescribed for the patient with support, an excipient, and other additives, and can be used for the therapy of the various diseases (for example, a nervous disease, cancer) of mammalian including Homo sapiens.

[0046] As oral pharmaceutical preparation, liquid preparations, such as solid-preparations; syrups, such as powder, a granule, a capsule, and a tablet, elixirs, and an emulsion, can be mentioned. It can mix with excipients, such as a lactose, starch, crystalline cellulose, a calcium lactate, calcium hydrogenphosphate, magnesium aluminometasilicate, and a silicic acid anhydride, and powder can be obtained. If needed besides the above-mentioned excipient, a granule can add further disintegrator, such as binders, such as white soft sugar, hydroxypropylcellulose, and a polyvinyl pyrrolidone, and a carboxymethyl cellulose, carboxymethyl-cellulose calcium, and can corn and obtain it by wet or dry type. A tablet can add lubricant, such as remaining as it is or magnesium stearate, and talc, and can tablet and obtain the above-mentioned powder or a granule. Moreover, the

above-mentioned tablet or a granule can be covered with enteric bases, such as hydroxypropylmethylcellulose phthalate, a methyl-methacrylate copolymer, hydroxypropyl-methylcellulose acetate, and hydroxypropyl-methylcellulose succinate, or can be covered with ethyl cellulose, a carnauba wax, hardened oil, white shellac, etc., and can make these enteric or durability pharmaceutical preparation. Hard capsules can fill up a hard filled capsule with the above-mentioned powder or a granule, and can obtain it. Moreover, an elastic capsule can dissolve this invention compound in a glycerol, a polyethylene glycol, sesame oil, olive oil, etc., and can cover and obtain this with the gelatin film. Syrups can be dissolved in water and can obtain a sweetening agent and this invention compounds, such as white soft sugar, a sorbitol, and a glycerol. Moreover, essential oil, ethanol, etc. are added other than a sweetening agent and water, it can consider as elixirs, or gum Arabic, tragacanth, polysorbates (polysorbate 20, polysorbate 60, polysorbate 80 (Tween 80), etc.), carboxymethylcellulose sodium, etc. can be added, and it can also be made an emulsion or suspension. Moreover, corrigent, a coloring agent, a preservative, etc. can be added to such liquid preparations if needed.

[0047] As parenteral pharmaceutical preparation, injections, a rectum administration agent, a pessary, skin external preparations, inhalations, aerosols, ophthalmic solutions, etc. can be mentioned. To this invention compound, after injections add stabilizing agent; and distilled water for injection, or physiological salines, such as pH regulator; sodium chlorides, such as nonionic surface active agent; hydrochloric acids, such as polysorbates, a sodium hydroxide, a lactic acid, sodium lactate, phosphoric-acid 1 hydrogen sodium, and a sodium dihydrogenphosphate, and grape sugar, and carry out sterilization filtration if needed, they can be filled up with and obtained at ampul. [, such as isotonizing agent; amino acid] furthermore, a mannitol, a dextran, gelatin, etc. -- adding -- freeze-drying -- business -- the time -- a dissolution mold -- it can consider as injections. In addition, it can also consider as the injections of a powder restoration mold. Moreover, after adding emulsifiers, such as lecithin, polysorbates, polyoxyethylene hydrogenated castor oil, and macro gall, to this invention compound, it can also be made the emulsion for injection made to emulsify underwater.

[0048] Moreover, as injections, liposome pharmaceutical preparation which can improve a shift rate, a lipid microsphere, etc. to solubility and a target organ are mentioned. It raises blood drug concentration, without a reticuloendothelial system organization being in confusion, and since a cerebral blood vessel gateway is made easy to pass about 10 times it not only to be able to to reduce the minimum effective dose required for a drug effect manifestation, but, especially NANOSU fair-liposome (lipid ultrafine particle) is suitable when using it for the therapy of a cerebral nervous disease. Liposome pharmaceutical preparation can be prepared according to the well-known liposome method of preparation (C. G.Knight, Liposomes: From Physical Structure to Therapeutic Applications, pp.51-82, Elsevier, Amsterdam; (1981) Proc.Natl.Acad.Sci., U.S.A., Vol.75, 4194 (1978)).

[0049] That is, as amphiphile which forms the liposome film, phospholipid, such as natural phospholipid (yolk lecithin, a soybean lecithin, sphingomyelin, phosphatidylserine, phosphatidylglycerol, phosphatidylinositol, diphosphatidyl glycerol, phosphatidylethanolamine, cardiolipin, etc.) and synthetic phospholipid (JISUTE aroyl phosphatidylcholine, dipalmitoylphosphatidylcholine, dipalmitoyl phosphatidylethanolamine, etc.), is used. in order [moreover,] to improve membranous stability, a fluidity, and the membrane permeability of drugs -- cholesterol (cholesterol --) An ergosterol, a phytosterol, a sitosterol, stigmasterol, etc., the matter (phosphatidic acid --) with which giving a negative charge to liposome is known Well-known various additives [, such as matter (a stearyl amine, stearyl amine acetate, etc.) with which giving positive charge is known, antioxidants (tocopherol etc.), and oily matter,] (soybean oil, cotton seed oil, sesame oil, liver oil, etc.), such as JISECHIRU phosphate, may be used.

[0050] Manufacture of liposome can be performed by the following approaches. The above-mentioned amphiphile and an additive, and this invention compound are dissolved in an organic solvent (independent or mixed solvents, such as chloroform, dichloromethane, ethanol, a methanol, and a hexane), respectively, both solutions are mixed, an organic solvent is removed under existence of inert gas (nitrogen gas, argon gas, etc.) in containers, such as a flask, and a thin film is made to adhere to a container wall. Subsequently, this thin film is added to suitable aquosity media (a physiological saline, buffer solution, phosphate buffered saline, etc.), and it agitates with an agitator. In order to obtain the liposome of the diameter of a granule, it is made to distribute further using an ultrasonic emulsifier, a pressurization mold emulsifier, French press cell homogenizer, etc. Thus, by carrying out membrane filter processing of the liquid which amphiphile required for liposome-izing etc. and this invention compound distributed to the aquosity medium, liposome-ization advances and the NANOSU fair-liposome (lipid ultrafine particle; particle size of about 25-50nm) by which particle size distribution was controlled can be obtained. Moreover, liposome may be given to fractionation processing of an ultrafiltration, centrifugal separation, gel filtration, etc., and the drugs which were not supported may be removed.

[0051] Moreover, a cerebral blood vessel gateway can also be made easy to pass by making the liposome which has

on the film the glucose residue obtained as a film morphogenetic substance by adding beta-octyl glucoside, the L-thyrosin-7-amide-4-methyl coumarin, the phenylamino mannoside, or sulfatide other than both the above-mentioned **** matter and an additive, thyrosin residue, mannose residue, or sulfatide support this invention compound (refer to JP,4-69332,A).

[0052] A lipid microsphere dissolves this invention compound in soybean oil, sesame oil, etc., adds natural phospholipid, a glycerol, water, etc., agitates them with an agitator, and is obtained by making it distribute using an ultrasonic emulsifier, a pressurization mold emulsifier, French press cell homogenizer, etc. further.

[0053] After a rectum administration agent adds bases for suppositories, such as monochrome of a cacao fatty acid, JI or a triglyceride, and a polyethylene glycol, to this invention compound, it is warmed and fused, and after it slushes this into a mold, and cools or dissolves this invention compound in a polyethylene glycol, soybean oil, etc., it can be covered and obtained with the gelatin film.

[0054] Skin external preparations can add white vaseline, yellow bees wax, a liquid paraffin, a polyethylene glycol, etc. to this invention compound, and can warm, knead and obtain them if needed.

[0055] A tape can knead binders, such as rosin and an acrylic-acid alkyl ester polymer, to this invention compound, and can spread and obtain this to a nonwoven fabric etc.

[0056] Inhalations can dissolve or distribute this invention compound to propellants, such as inert gas permitted by for example, the pharmaceutical-sciences target, and can fill up with and obtain this in a proof-pressure container at them.

[0057] When using this invention compound as the therapy agent of a nervous disease especially a brain protective agent, or cranial nerve activation and a protective agent, injections are desirable and an intravenous injection agent is more desirable. Such injections are good also as pharmaceutical preparation which contains lipid microsphere pharmaceutical preparation and a surfactant in consideration of the brain internal transmigration nature of this invention compound.

[0058] [Medication method] Although especially the medication method of the drugs which contain this invention compound as an active principle is not limited, when using it for the therapy of the nervous disease resulting from the failure of a central nervous system, and an intramuscular injection, an intravenous injection, subcutaneous injection, or intraperitoneal injection passes, and rectum administration, transpulmonary administration, instillation, etc. are desirable [intraperitoneal injection etc.]. although a dose is suitably determined according to a patient's age, health condition, weight, etc. -- general -- 0.25 - 200 mg/kg -- desirable -- 0.5 - 100 mg/kg It divides more than one day or it, and a medicine is prescribed for the patient.

[0059] [Toxicity] this invention compound (hydrochloride) of an example 1-2 and the safety of an L-threo-PDMP hydrochloride (compound of the example 4-2 of preparation) were examined using the 5-weeks old Wister system rat. The injections which contain each compound 1.5% to 2.5%, using a Tween 80 content physiological saline as an excipient (Vehicle) are prepared, and it is an intravenous injection (i. v.) to the above-mentioned rat. The result prescribed for the patient is shown in Table 1.

[0060]

[Table 1]

	LD ₅₀ 値 (i. v.)	2週反復i. v.投与での無影響量*
L-トレオ-PDMP塩酸塩	80mg/kg	10mg/kg**
実施例1-2 の化合物 (塩酸塩)	91mg/kg	20mg/kg**

* 反復投与後の一般状態、体重、摂餌量、尿検査、血液学的検査、剖検及び肝臓・腎臓の組織学的検査の全てに異常が認められない、安全性を示す投与量。

** 2化合物とともに40mg/kgの2週反復i. v.投与において、投与直後の一過性の神経症状が認められたが、特に実施例1-2の化合物は、体重、摂餌量、尿検査、血液学的検査、剖検及び肝臓・腎臓の組織学的検査において正常であった。

[0061]

[Example] Next, although an example explains this invention to a detail further, unless the summary is exceeded, this invention is limited to the following examples and is not a thing. In addition, the synthetic example of intermediate field is shown as an example of preparation.

[0062] Example 1 of preparation (1S, 2S) After melting synthetic (1S, 2S) -2-benzyloxycarbonylamino-1-phenyl-1,3-propanediol 15.4g (51.0mmol) of -2-benzyloxycarbonylamino-1-phenyl-1,3-propanediol-3-methane sulfonyl ester to 150ml of methylene chlorides and adding pyridine 12.1ml (149.6mmol), it was dropped on the ice bath, having methane sulfonyl chloride 4.5 bet it for 5 minutes (58.1mmol). After agitating for 30 minutes on an ice bath, it agitated at the room temperature overnight. After checking that the reaction is completed by TLC (chloroform: methanol =20:1, hexane:ethyl-acetate =1:1), 100ml [of water] and chloroform 50ml is added, and it is 1 N about an organic layer. After carrying out sequential washing by the hydrochloric acid, water, the saturation sodium-hydrogencarbonate solution, and 100ml of each water, it dried and filtered on the sodium sulfate. The solvent was distilled off, n-hexane:ethyl-acetate =2:1 (100ml) was added and overnight neglect was carried out. The depositing crystal was ****(ed), it washed by KISAN:ethyl-acetate =2:1 to n-, and 16.6g (85.7% of yield) of mark matter of a white crystal was obtained.

[0063] Example 2 of preparation (1S, 2S) Synthetic (1S, 2S) -2-benzyloxycarbonylamino-1-phenyl-1,3-propanediol-3-methane sulfonyl ester 1.21g (3.19mmol) of -2-benzyloxycarbonylamino-3-morpholino-1-phenyl-1-propanol was melted to 6ml of N,N-dimethylformamide, morpholine 1.11g (12.8mmol) was added under the room temperature, and it agitated at 40 degrees C for 24 hours. After checking that the reaction is completed mostly by TLC (chloroform: methanol =20:1, n-hexane:ethyl-acetate =1:2, ethyl acetate), 70ml of saturation sodium-hydrogencarbonate solutions and 100ml of ethyl acetate were added, sequential washing of the organic layer was carried out with water and each saturation brine, and it dried and filtered on the sodium sulfate. The solvent was distilled off, the silica gel column chromatography (n-hexane: ethyl-acetate =1:2) refined residue, and 507.5mg (43.0% of yield) of colorless oil-like mark matter was obtained.

[0064] Example 3 of preparation (1S, 2S) Synthetic (1S, 2S) -2-benzyloxycarbonylamino-3-morpholino-1-phenyl-1-propanol 438.8mg (1.19mmol) of -2-amino-3-morpholino-1-phenyl-1-propanol was melted to methanol 10ml, 126.5mg (10.0mol %) of palladium carbon was added 10%, and overnight churning was carried out at the room temperature under the hydrogen ambient atmosphere. After checking that the reaction is completed by TLC (chloroform: methanol = 9:1 and 7:3), filtration removal of the palladium carbon was carried out. The filtrate was condensed and 275.6mg (98.5% of yield) of colorless oil-like mark matter was obtained.

[0065] Example 4-1 of preparation (1S, 2S) Synthetic (1S, 2S) -2-amino-3-morpholino-1-phenyl-1-propanol 944.0mg (4.00mmol) of -2-decanoylamino-3-morpholino-1-phenyl-1-propanol was melted to methanol 4ml, triethylamine 668.0microl (4.8mmol) was added, and decanoyl chloride 0.82ml (4.0mmol) was dropped under ice-cooling. After 30 minutes, after checking that the reaction is almost completed by TLC (ethyl acetate, chloroform:methanol =20:1, a chloroform:methanol = 7:3), methanol 30ml was added and it was left for 90 minutes. 20ml of saturation sodium-hydrogencarbonate solutions was added after vacuum concentration, and 50ml of ethyl acetate extracted the reaction solution. The organic layer was dried and filtered on the sodium sulfate after sequential washing by water and 20ml of each saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (ethyl acetate) refined the obtained rough product, and 930.5mg (59.6% of yield) of colorless oil-like mark matter was obtained.

[0066] Example 4-2 of preparation (1S, 2S) -2 - It is 2 Ns to the preparation (1S, 2S)-2-decanoylamino-3-morpholino-1-phenyl-1-propanol (179g, 459.0mmol) of a decanoylamino-3-morpholino-1-phenyl-1-propanol hydrochloride. The hydrochloric acid (250ml) was added and overnight neglect was carried out under ice-cooling. come out of the depositing crystal on a glass filter -- it **(ed), and with water (100mlx5) and the ether (100mlx5), after sequential washing, reduced pressure drying was carried out for bottom 48 hours of a room temperature, and the 1S and (2S)-2-decanoylamino-3-morpholino-1-phenyl-1-propanol hydrochloride (98.0g, 50.0% of yield) of a white crystal was obtained.

[0067] Example 5 of preparation () 1S, 2S-2 - -(1S, 2S)2-amino-3-morpholino-1-phenyl-1-propanol 627.7mg (2.66mmol) obtained in the example 3 of synthetic preparation of octyloxy carbonylamino-3-morpholino-1-phenyl-1-propanol It melted to methanol 10ml, and the bottom of a room temperature, and after adding triethylamine 0.518ml (3.723mmol), KUROROGI acid n-octyl ester 0.625ml (3.19mmol) was added on the ice bath, and it agitated under the room temperature for 15 hours. After reaction termination and after adding methanol 5ml and agitating for 20 minutes, reduced pressure distilling off of the solvent was carried out, 100ml of ethyl acetate was added, the organic layer was dried and filtered on the sodium sulfate after sequential washing by the saturation sodium-hydrogencarbonate solution, water, and 70ml of each saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (n-hexane: ethyl-acetate =1:2) refined the obtained rough product, and 814.5mg (78.1% of yield) of colorless oil-like mark matter was obtained.

TLC Rf 0.21 (n-Hexane:AcOEt=1: 2), 0.32 (CHCl₃:MeOH=20:1) and 0.36(AcOEt) 1 H-NMR (CDCl₃) delta:

7.38-7.26 (5H, m, aromatic), 4.99 (1H, d, J= 3.42Hz, H--1) 4.08 (1H, m, H-2), 3.98 (2H, m, COOCH₂) 3.73 (4H, m, 2(CH₂) O), 2.66-2.45 (6H, m, CH₂N₂ (CH₂)), 1.54 (2H, m, COOCH₂CH₂), 1.27 (10H, m, 5(CH₂) CH₃), 0.88 (3H, t, CH₂CH₃) 13C-NMR(CDCl₃) delta: 156.5, 140.7, 128.3, 127.6, 126.2, 75.4, 66.9, 65.3, 60.1, 54.4, and 52.0, the fifty percent lethal dose value (i. v. administration) of this compound measured by 31.7, 29.2, 29.0, 28.9, 25.7, 22.6, and the approach (refer to Table 1) of the 14.0 above and the same approach -- 69 mg/kg it is -- the no-observed effect level (dose which shows the safety abnormalities are not accepted to be to all the histological inspection of the general status after repeated-dose administration, weight, the amount of baiting, a urinalysis, hematology-inspection, an autopsy, and the liver and the kidney) in two-week repeated-dose administration -- 20 mg/kg it was .

[0068] Example 6 of preparation () 1R, synthetic (R [1], 2R) -2-benzyloxycarbonylamino-1-phenyl-1,3-propanediol-3-methane sulfonyl ester 1.52g of 2R-2-benzyloxycarbonylamino-3-pyrrolidino-1-phenyl-1-propanol (4.01mmol) is melted to 8ml (DMF) of N,N-dimethylformamide. After adding pyrrolidine 1.14g (16.0mmol) and agitating at 40-50 degrees C for 18 hours, 100ml of ethyl acetate was added, the organic layer was dried and filtered on the sodium sulfate after sequential washing by the saturation sodium-hydrogencarbonate solution, water, and 70ml of each saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (chloroform: methanol =20:1) refined the obtained rough product, and 1.21g (85.5% of yield) of colorless oil-like mark matter was obtained.

[0069] Example 7 of preparation () the synthetic (1) (4S, 5S)-5-(1-(E)-hexenyl)-4-hydroxymethyl-2-nonyl-2-oxazoline (2S and 3S --) of 2S, 3S, and 4E-2-decanoylamino-1-morpholino-4-nonene-3-oar Methane sulfonyl chloride 0.65ml (8.43mmol) was dropped at the 4E-2-decanoylamino-4-nonene -1 and 3-diol 2.3g (7.02mmol) pyridine 10ml solution at 0 degree C under nitrogen-gas-atmosphere mind. At 0 degree C, morpholine 6.1ml (70.2mmol) was added after 1-hour churning, and it agitated for 44 hours. Ethyl acetate extracted 3 times, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (CH₃ Cl) refined the obtained rough product, and 1.46g (67% of yield) of mark matter was obtained.

1H-NMR(CDCl₃; D₂O exchange): 5.77(1H, dt, J=15.5, 6.6Hz, =CH-CH₂), 5.49(1H, dd, J=15.5, 8.3Hz, CH-CH=), 4.69(1H, t, J=8.3Hz, O-CH), 3.80(2H, m), 3.50(1H, m, CH-OH), 2.27(2H, t, J=7.6Hz, N=C-CH₂), 2.07(2H, q, J=6.6Hz, =CH-CH₂), 1.62(2H, m), 1.26(16H,m, 0.89 (6H, m, CH₃) TOF-Mass: 310 (M+H⁺), 333 (M+Na⁺H⁺) HRMS(C19H35NO₂ 309) (FAB) C19H36NO₂ (M+H⁺), Theoretical value; 310.2746 Measured value; 310.2750 [alpha] D23=-75.9 ** (c= 1.10, CHCl₃) [0070] (2) 4S, (5S)-5- In (1-(E)-hexenyl)-4-MORIHORINO methyl-2-nonyl-2-oxazoline (4S, 5S)-5-(1-(E)-hexenyl)-4-hydroxymethyl-2-nonyl-2-oxazoline 700mg (2.26mmol) 15ml solution of methylene chlorides At -45 degrees C, pyridine 0.55ml (6.79mmol) and 0.46ml (2.71mmol) of anhydrous trifluoroacetic acid were dropped under nitrogen-gas-atmosphere mind. - Morpholine 1.98ml (22.6mmol) was added after 1-hour churning at 45 degrees C. - It extracted at 45 degrees C for 1 hour, ethyl acetate extracted 3 times after 2-hour churning at the room temperature, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (n-hexane: ethyl-acetate =2:1) refined the obtained rough product, and 141.0mg (39% of yield) of mark matter was obtained.

1H-NMR(CDCl₃): 5.76(1H, dt, J=15.2,6.9Hz, =CH-CH₂), 5.46(1H, dd, J=15.2,7.6Hz, CH-CH=), 4.62(1H, t, J=7.6Hz, O-CH),3.87(1H, q, J=6.9Hz, N-CH), 3.68(4H, m, (CH₂)₂O),2.63-2.32(6H, m, CH₂N(CH₂)₂), 2.26(2H, t, J=8.0Hz, N=C-CH₂), 2.06(2H, m, =CH-CH₂), 1.61(2H, m, 1.26 (16H, m), 0.89 (6H, m, CH₃) 13 C-NMR (CDCl₃) : 167.7, 134.7, 128.1, 84.5, 69.7, 66.7, 62.9, 54.0, 31.7, 31.0, 29.3, and 29.1, 29. 0, 28.2, 25.9, 22.5, 22.0, 14.0, 13.7 TOF-Mass: 379 (M+H⁺), HRMS(C23H42N2O₂ 378) (FAB) C23H43N 2O₂ (M+H⁺) Theoretical value; 379.3325 Measured value; 379.3322[alpha] D23=-38.4 ** (c= 1.00, CHCl₃) [0071] (3) 2S, 3S, and (E[4]) -2-decanoylamino-1-morpholino-4-nonene-3-all (4S, 5S)-5-(1-(E)-hexenyl)-4 - It is 3 Ns to MORIHORINO methyl-2-nonyl-2-oxazoline 39mg (0.103mmol). 3ml of hydrochloric acids was added and it agitated at the room temperature for 13 hours. After adjusting to pH9 by 1N NaOH, ethyl acetate extracted 3 times, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (n-hexane: ethyl-acetate =1:3) refined the obtained rough product, and 24.5mg (60% of yield) of mark matter was obtained.

1H-NMR(CDCl₃; D₂O exchange): 5.73(1H, dt, J=15.5, 6.6Hz, H-5), 5.42(1H, dd, J=15.2, 6.3Hz, H-4), 4.28(1H, dd, J=5.9, 3.3Hz, H-3), 4.05(1H, m,H-2), 3.69(4H, t, J=4.6Hz, (CH₂)₂O), 2.69(1H, dd, J=13.2, 6.6Hz, H-1a), 2.56 (4H, t, J=4.6Hz, N(CH₂)₂), 2.51(1H, dd, J= 13.2, 5.9 Hz, H-1b, 2.17 (2H, t, J= 7.9Hz, CO-CH₂) 2.06 (2H, m, =CH-CH₂), 1.60 (2H, m) 1.26 (16H, m), 0.89 (6H, m, CH₃) 13 C-NMR (CDCl₃) : 173.5, 133.5, 128.8, 73.5, 66.7,

59.6, 54.1, 49.8, 36.7, 31.9, 31.2, 29.3, and 29.1, 25.7, 22.5, 22.1, 14.0, 13.8 TOF-Mass: 397 (M+H⁺), 420 (M+Na⁺) (C₂₃H₄₄N₂O₃ 396) HRMS(FAB) C₂₃H₄₅N₂O₃ (M+H⁺) Theoretical value; 397.3430 Measured value; 397.3430[alpha] D23=-23.3 ** (c= 0.49, CHCl₃) [0072] Example 8 of preparation () the synthetic (1) (4S, 5S)-5-(1-(E)-PENTA decenyl)-4-hydroxymethyl-2-nonyl-2-oxazoline (2S and 3S --) of 2S, 3S, and 4E-2-decanoylamino-1-morpholino-4-octadecene-3-oar Methane sulfonyl chloride 0.55ml (7.11mmol) was dropped at the 4E-2-decanoylamino-4-octadecene -1 and 3-diol 2.48g (5.47mmol) pyridine 20ml solution at 0 degree C under nitrogen-gas-atmosphere mind. At 0 degree C, morpholine 4.8ml (54.7mmol) was added after 1-hour churning, and it agitated under the room temperature for 15 hours. Chloroform extracted 3 times, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. Filtration removal of the crystal which added the hexane to the obtained rough product and deposited was carried out, the silica gel column chromatography (CH₃ Cl) refined the filtrate after vacuum concentration, and 1.64g (69% of yield) of mark matter was obtained.

1H-NMR(CDCl₃; D₂O exchange): 5.77(1H, dt, J=15.3, 6.6Hz, =CH-CH₂), 5.48(1H, dd, J=15.3, 8.1Hz, CH-CH=), 4.70(1H, t, J=8.1Hz, O-CH), 3.80(2H, m, CH-OH, N-CH), 3.49(1H, dd, J=11.6, 4.3Hz, CH-OH), 2.26(2H, t, J=7.9Hz,N=C-CH₂), 2.05(2H, q, J=6.6Hz, =CH- CH₂, 1.61 (2H, m, N=C-CH₂-CH₂) 1.26 (34H, m), 0.88 (6H, t, J= 6.9Hz, CH₃) 13 C-NMR (CDCl₃) : 169.0, 135.6, 127.5, 82.4, 73.4, 62.6, 32.1, 31.8, 29.5, and 29.3, 29.2, 29.1, 29.0, 28.7, 28.2, 25.9, 22.6, 14.0 TOF-Mass: 436 (M+H⁺) 459 (M+Na⁺H⁺), HRMS(C₂₈H₅₃NO₂ 435) (FAB) C₂₈H₅₄NO₂ (M+H⁺), Theoretical value; 436.4155 Measured value; 436.4147[alpha] D23=-54.4 ** (c= 1.00, CHCl₃) [0073] (2) 4S, (5S)-5- () [1-] (E) in - PENTA decenyl-4-morpholino methyl-2-nonyl-2-oxazoline (4S, 5S)-5-(1-(E)-PENTA decenyl)-4-hydroxymethyl-2-nonyl-2-oxazoline 1.58g (3.63mmol) 200ml solution of methylene chlorides At -45 degrees C, pyridine 0.88ml (10.9mmol) and 0.73ml (4.35mmol) of anhydrous trifluoroacetic acid were dropped under nitrogen-gas-atmosphere mind. - Morpholine 3.2ml (36.3mmol) was added after 2-hour churning at 45 degrees C. - It extracted at 45 degrees C for 2 hours, chloroform extracted 3 times after 8-hour churning at the room temperature, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (n-hexane: ethyl-acetate =3:1) refined the obtained rough product, and 432mg (24% of yield) of mark matter was obtained.

1H-NMR(CDCl₃): 5.75(1H, dt, J=15.2, 6.9Hz, =CH-CH₂), 5.46(1H, dd, J=15.2, 7.6Hz, CH-CH=), 4.62(1H, t, J=7.6Hz, O-CH), 3.87(1H, q, J=6.9Hz, N-CH), 3.68(4H, m, (CH₂)₂O), 2.63-2.32(6H, m, CH₂N(CH₂)₂), 2.26(2H, t, J=8.0Hz, N=C-CH₂), 2.05(2H, q, J=6.9Hz, =CH-CH₂, 1.62 (2H, m, N=C-CH₂-CH₂), 1.26 (34H, m), 0.88 (6H and t -- J= 6.9Hz) CH₃ 13 C-NMR(CDCl₃): 167.8, 134.8, 128.1, and 84.5, 69.7, 66.8, 62.9, 54.1, 32.1, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.9, 28.3, 26.0, 22.6, 14.0 TOF-Mass: 505 (M+H⁺), HRMS(C₃₂H₆₀N₂O₂ 504) (FAB) C₃₂H₆₁N₂O₂ (M+H⁺) Theoretical value; 505.4733 Measured value; 505.4736[alpha] D23=-18.8 degree (c= 1.00, CHCl₃) [0074] (3) 2S, 3S, and (E[4]) -2-decanoylamino-1-morpholino-4-octadecene-3-all (4S, 5S)-5-(1-(E)-PENTA decenyl)-4 - It is 3 Ns to morpholino methyl-2-nonyl-2-oxazoline 314mg (0.62mmol). 3ml of hydrochloric acids was added and it agitated at the room temperature for 2 hours. After adding 1N NaOH to reaction mixture and adjusting to pH9, ethyl acetate extracted 3 times, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (n-hexane: ethyl-acetate =1:4) refined the obtained rough product, and 187.0mg (58% of yield) of mark matter was obtained.

1H-NMR(CDCl₃; D₂O exchange): 5.73(1H, dt, J=15.2, 6.9Hz, H-5), 5.42(1H, dd, J=15.2, 6.3Hz, H-4), 4.27(1H, dd, J=6.3, 3.6Hz, H-3), 4.04(1H, m,H-2), 3.69(4H, t, J=4.6Hz, (CH₂)₂O), 2.69(1H, dd, J=12.9, 6.6Hz, H-1b), 2.55 (4H, t, J=4.6Hz,N(CH₂)₂), 2.49(1H, dd, J= 12.9, 5.6 Hz, H-1b, 2.17 (2H, t, J= 7.6Hz, CO-CH₂) 2.04 (2H, q, J= 6.6Hz, =CH-CH₂), 1.60 (2H, m, CO-CH₂-CH₂) 1.26 (34H, m), 0.88 (6H, t, J= 6.9Hz, CH₃) 13 C-NMR (CDCl₃) : 173.4, 133.5, 128.8, 73.6, 66.8, 59.7, 54.2, 49.8, 36.7, and 32.2, 31.8, 31.7, 29.6, 29.4, 29.3, 29.2, 25.7, 22.5, 14.0 TOF-Mass: 524 (M+H⁺), 546(M+Na⁺) (C₃₂H₆₂N₂O₃ 522) HRMS(FAB) C₃₂H₆₃N₂O₃ (M+H⁺) Theoretical value; 523.4838 Measured value; 523.4837[alpha] D23=-17.6 ** (c= 1.00, CHCl₃) [0075] Example 9 of preparation () 2R, 3R, the 4E-decanoylamino-1-morpholino-4-nonene-3-all (1) (R [4],R [5])-5-(1-(E)-hexenyl)-4-hydroxymethyl-2-nonyl-2-oxazoline (R [2],R [3], 4E)-2-decanoylamino-4-nonene -1, Triethylamine 128microl (0.916mmol) and methane sulfonyl chloride 28microl (0.366mmol) were dropped at 3-diol 88.8mg (0.305mmol) 2ml solution of methylene chlorides at 0 degree C under nitrogen-gas-atmosphere mind. They are after 1-hour churning and a morpholine (267microl (3.05mmol) was added and it agitated at the room temperature for 19 hours.) at 0 degree C. Ethyl acetate extracted 3 times, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel

column chromatography (CH₃ Cl) refined the obtained rough product, and 48.5mg (51% of yield) of mark matter was obtained.

1H-NMR(CDCI₃; D₂O exchange): 5.77(1H, dt, J=15.5, 6.6Hz, =CH-CH₂), 5.49(1H, dd, J=15.5, 8.3Hz, CH-CH=), 4.69(1H, t, J=8.3Hz, O-CH), 3.80(2H, m), 3.50(1H, m, CH-OH), 2.27(2H, t, J=7.6Hz, N=C-CH₂), 2.07(2H, q, J=6.6Hz, =CH-CH₂), 1.62(2H, m), 1.26(16H,m, 0.89 (6H, m, CH₃) TOF-Mass: 310 (M+H⁺), 333 (M+Na⁺H⁺) HRMS(C₁₉H₃₅NO₂ 309) (FAB) C₁₉H₃₆NO₂ (M+H⁺), Theoretical value; 310.2746 Measured value; 310.2750 [alpha]D₂₃=+75.9 ** (c= 1.10, CHCl₃) [0076] (2) 4R, (R[5]) 5- In (1-(E)-hexenyl)-4-morpholino methyl-2-nonyl-2-oxazoline (R [4], 5R)-5-(1-(E)-hexenyl)-4-hydroxymethyl-2-nonyl-2-oxazoline 298.0mg (0.963mmol) 2ml solution of methylene chlorides At -45 degrees C, pyridine 234microl (2.89mmol) and 194micro [of anhydrous trifluoroacetic acid] 1 (1.16mmol) were dropped under nitrogen-gas-atmosphere mind. - Morpholine 0.84ml (9.63mmol) was added after 1.5-hour churning at 45 degrees C. - It extracted at 45 degrees C for 1 hour, ethyl acetate extracted 3 times after 2-hour churning at the room temperature, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (n-hexane: ethyl-acetate =3:1) refined the obtained rough product, and 141.0mg (39% of yield) of mark matter was obtained.

1H-NMR(CDCI₃): 5.76(1H, dt, J=15.2, 6.9Hz, =CH-CH₂), 5.46(1H, dd, J=15.2, 7.6Hz, CH-CH=), 4.62(1H, t, J=7.6Hz, O-CH), 3.87(1H, q, J=6.9Hz, N-CH), 3.68(4H, m, (CH₂)₂O), 2.63-2.32(6H, m, CH₂N(CH₂)₂), 2.26(2H, t, J=8.0Hz, N=C-CH₂), 2.06(2H, m, =CH-CH₂), 1.61 (2H, m), 1.26 (16H, m), 0.89 (6H, m, CH₃) 13 C-NMR (CDCI₃) : 167.7, 134.7, 128.1, 84.5, 69.7, 66.7, 62.9, 54.0, 31.7, 31.0, and 29.3, 29. 1, 29.0, 28.2, 25.9, 22.5, 22.0, 14.0, 13.7 TOF-Mass: 379 (M+H⁺), HRMS(C₂₃H₄₂N₂O₂ 378) (FAB) C₂₃H₄₃N₂O₂ (M+H⁺) Theoretical value; 379.3325 Measured value; 379.3322[alpha]D₂₃=+32.5 ** (c= 0.43, CHCl₃) [0077] (3)R [2],R [3], and (E[4])-2-decanoylamino-1-morpholino-4-nonene-3-all (R [4], 5R)-5-(1-(E)-hexenyl)-4 - It is 3 Ns to morpholino methyl-2-nonyl-2-oxazoline 174.0mg (0.46mmol). 3ml of hydrochloric acids was added and it agitated at the room temperature for 13 hours. After adding 1N NaOH to the reaction solution and adjusting to pH9, ethyl acetate extracted 3 times, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (n-hexane: ethyl-acetate =1:3) refined the obtained rough product, and 106.4mg (59% of yield) of mark matter was obtained.

1H-NMR(CDCI₃;D₂O exchange): 5.73(1H, dt, J=15.5, 6.6Hz, H-5), 5.42(1H,dd, J=15.2, 6.3Hz, H-4), 4.28(1H, dd, J=5.9, 3.3Hz, H-3), 4.05(1H, m, H-2), 3.69(4H, t, J=4.6Hz, (CH₂)₂O), 2.69(1H, dd, J=13.2, 6.6Hz, H-1a), 2.56(4H, t, J=4.6Hz, N(CH₂)₂), 2.51(1H, dd, J= 13.2, 5.9 Hz, H-1b, 2.17 (2H, t, J= 7.9Hz, CO-CH₂) 2.06 (2H, m, =CH-CH₂), 1.60 (2H, m) 1.26 (16H, m), 0.89 (6H, m, CH₃) 13 C-NMR (CDCI₃) : 173.5, 133.5, 128.8, 73.5, 66.7, 59.6, 54.1, 49.8, 36.7, 31.9, and 31.2, 29. 3, 29.1, 25.7, 22.5, 22.1, 14.0, 13.8 TOF-Mass: 397 (M+H⁺), 420(M+Na⁺) (C₂₃H₄₄N₂O₃ 396) HRMS(FAB) C₂₃H₄₅N₂O₃ (M+H⁺) Theoretical value; 397.3430 Measured value; 397.3430 [alpha]D₂₃=+23.0 ** (c= 1.00, CHCl₃) [0078] Example 10 of preparation () the synthetic (1) (R [4],R [5]) 5-(1-(E)-PENTA decenyl)-4-hydroxymethyl-2-nonyl-2-oxazoline (2R and 3R --) of 2R, 3R, and 4E-2-decanoylamino-1-morpholino-4-octadecene-3-oar Methane sulfonyl chloride 0.33ml (4.26mmol) was dropped at the 4E-2-decanoylamino-4-octadecene -1 and 3-diol 1.38g (3.04mmol) pyridine 10ml solution at 0 degree C under nitrogen-gas-atmosphere mind. At 0 degree C, morpholine 2.7ml (30.4mmol) was added after 2-hour churning, and it agitated under the room temperature for 18 hours. Chloroform extracted 3 times, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. Filtration removal of the crystal which added the hexane to the obtained rough product and deposited was carried out, the silica gel column chromatography (CH₃ Cl) refined the filtrate after vacuum concentration, and 496mg (37% of yield) of mark matter was obtained.

1H-NMR(CDCI₃, D₂O exchange): 5.77(1H, dt, J=15.3, 6.6Hz, =CH-CH₂), 5.48(1H, dd, J=15.3, 8.1Hz, CH-CH=), 4.70(1H, t, J=8.1Hz, O-CH), 3.80(2H, m, CH-OH, N-CH), 3.49(1H, dd, J=11.6, 4.3Hz, CH₂-OH), 2.26(2H, t, J=7.9Hz, N=C-CH₂), 2.05(2H, q, J=6.6Hz, =CH-CH₂), 1.61 (2H, m, N=C-CH₂-CH₂) 1.26 (34H, m), 0.88 (6H and t -- J= 6.9Hz) CH₃13C-NMR(CDCI₃): 169. 0, 135.6, and 127.5, 82. 4, 73.4, 62.6, 32.1, 31.8, 29.5, 29.3, 29.2, 29.1, 29.0, 28.7, 28.2, 25.9, 22.6, 14.0 TOF-Mass: 436 (M+H⁺) 459 (M+Na⁺H⁺), HRMS(C₂₈H₅₃NO₂ 435) (FAB) C₂₈H₅₄NO₂ (M+H⁺) Theoretical value; 436.4155 Measured value; 436.4147[alpha]D₂₃=+54.7 ** (c= 2.94, CHCl₃) [0079] (2) 4R, (R[5]) 5- () [1-] (E) in - PENTA decenyl-4-morpholino methyl-2-nonyl-2-oxazoline (R [4], 5R)-5-(1-(E)-PENTA decenyl)-4-hydroxymethyl-2-nonyl-2-oxazoline 802mg (1.84mmol) 40ml solution of methylene chlorides At -45 degrees C, pyridine 0.45ml (5.52mmol) and 372micro [of anhydrous trifluoroacetic acid] 1 (2.21mmol) were dropped under nitrogen-gas-atmosphere mind. - Morpholine 1.61ml (18.4mmol) was added after 2-hour churning at 45 degrees C. - It extracted at 45 degrees C for 1 hour, chloroform extracted 3 times

after 5-hour churning at the room temperature, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (n-hexane: ethyl-acetate =3:1) refined the obtained rough product, and 219mg (24% of yield) of mark matter was obtained.

1H-NMR(CDCl₃): 5.75(1H, dt, J=15.2,6.9Hz, =CH-CH₂), 5.46(1H, dd, J=15.2,7.6Hz, CH-CH=), 4.62(1H, t, J=7.6Hz, O-CH), 3.87(1H, q, J=6.9Hz, N-CH), 3.68(4H, m, (CH₂)₂O), 2.63-2.32(6H, m, CH₂N(CH₂)₂), 2.26(2H, t, J=8.0Hz, N=C-CH₂), 2.05(2H, q, J=6.9Hz, =CH-CH₂, 1.62 (2H, m, N=C-CH₂-CH₂) 1.26 (34H, m), 0.88 (6H and t -- J= 6.9Hz) CH₃¹³C-NMR(CDCl₃): 167.8, 134.8, and 128.1, 84.5, 69.7, 66.8, and 62.9, 54.1, 32.1, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.9, 28.3, 26.0, 22.6, 14.0 TOF-Mass: 505 (M+H⁺), HRMS(C₃₂H₆₀N₂O₂ 504) (FAB) C₃₂H₆₁N₂O₂ (M+H⁺) Theoretical value; 505.4733 Measured value; 505.4736[alpha]D23=+19.4 ** (c= 0.32, CHCl₃) [0080] (3)R [2],R [3], and (E[4])-2-decanoylamino-1-morpholino-4-octadecene-3-all (R [4], 5R)-5-(1-(E)-PENTA decenyl)-4 - It is 3 Ns to morpholino methyl-2-nonyl-2-oxazoline 190mg (0.38mmol). 3ml of hydrochloric acids was added and it agitated at the room temperature for 2 hours. After adding 1N NaOH to reaction mixture and adjusting to pH9, ethyl acetate extracted 3 times, the organic layer was dried and filtered on magnesium sulfate after washing with saturation brine, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (n-hexane: ethyl-acetate =1:3) refined the obtained rough product, and 125mg (63% of yield) of mark matter was obtained.

1H-NMR(CDCl₃;D₂O exchange): 5.73(1H, dt, J=15.2, 6.9Hz, H-5), 5.42(1H,dd, J=15.2, 6.3Hz, H-4), 4.27(1H, dd, J=6.3, 3.6Hz, H-3), 4.04(1H, m, H-2), 3.69(4H, t, J=4.6Hz, (CH₂)₂O), 2.69(1H, dd, J=12.9, 6.6Hz, H-1b), 2.55(4H, t, J=4.6Hz, N(CH₂)₂), 2.49(1H, dd, J= 12.9, 5.6 Hz, H-1b, 2.17 (2H, t, J= 7.6Hz, CO-CH₂) 2.04 (2H, q, J= 6.6Hz, =CH-CH₂), 1.60 (2H, m, CO-CH₂-CH₂) 1.26 (34H, m), 0.88 (6H and t -- J= 6.9Hz) CH₃¹³C-NMR(CDCl₃): 173.4, 133.5 and 128.8, 73.6, 66.8, 59.7, 54.2, 49.8, 36.7, 32.2, 31.8, 31.7, 29.6, 29.4, 29.3, 29.2, 25.7, 22.5, 14.0 TOF-Mass: 524 (M+H⁺), 546(M+Na⁺) (C₃₂H₆₂N₂O₃ 522) HRMS(FAB) C₃₂H₆₃N₂O₃ (M+H⁺) Theoretical value; 523.4838 Measured value; 23= +16.9 degrees (c= 0.95, CHCl₃) of 523.4837[alpha] D

[0081] Example 1-1 (1S, 2S) -2-decanoylamino-3-morpholino-1-phenyl-1-propyl Composition -2 of acetate (1S, 2S) - 10.00g (22.47mmol) of decanoylamino-3-morpholino-1-phenyl-1-propanol hydrochlorides was melted to 220ml of methylene chlorides, under the room temperature, pyridine 9.10ml (112.51mmol) and 8.50ml (90.17mmol) of acetic anhydrides were added, and overnight churning was carried out. They are water and 1 N about the organic layer after adding a saturation sodium-hydrogencarbonate solution and agitating for 30 minutes after reaction termination. Sequential washing was carried out by a hydrochloric acid, water, the saturation sodium-hydrogencarbonate solution, water, and 150ml of each saturation brine, the organic layer was filtered after desiccation on the sodium sulfate, and reduced pressure distilling off of the solvent was carried out. It was left under the room temperature after dissolving the obtained rough product in the mixed solvent of a hexane and ethyl acetate, the depositing crystal was *****(ed), and 5.35g (55.2% of yield) of mark matter of a white crystal was obtained.

TLC Rf.0.23 (ethyl acetate), 0.36 (chloroform: methanol =20:1)

1 H-NMR (CDCl₃) : 7.35-7.26 (5H, m, aromatic), 6.05 (1H, d, J= 4.88Hz, H-1) 5.57 (1H, d, J= 9.28Hz, NH), 4.51 (1H, m, H-2) 3.64 (4H, m, 2(CH₂) O), 2.49-2.39 And 2.38-2.29 (6H, m, CH₂N₂ (CH₂)), 2.18-2.06 (5H, m, COCH₃, COCH₂), 1.54 (2H, m, COCH₂CH₂) 1.25 (12H, m, 6(CH₂) CH₃), 0.88 (3H, t, CH₂CH₃) 13 C-NMR (CDCl₃) : 172.8, 169.9, 137.6, 128.5, 128.2, 126.5, 75.0, 67.0, 59.1, and 53.9, 50.4, 36.8, 31.8, 29.4, 29.3, 29.2, 25.7, 22.6, 21.0, 14.1 [0082] example 1-2 (1S, 2S) -2-decanoylamino-3-morpholino-1-phenyl-1-propyl Preparation (1S, 2S)-2-decanoylamino-3-morpholino-1-phenyl-1-propyl of an acetate hydrochloride and other salts acetate 1,414.6 mg (3.275mmol) is melted to ethanol 30ml, and it is 2 Ns under a room temperature. After adding 1,638micro (3.276mmol) of hydrochloric acids l and agitating for 10 minutes, reduced pressure distilling off of the solvent was carried out. The actuation which adds ethanol 30ml after this and carries out reduced pressure distilling off was repeated 3 times, and carried out reduced pressure drying for bottom 48 hours of a room temperature, and 1.54g (100% of yield) of white *****-like 1S and (2S)-2-decanoylamino-3-morpholino-1-phenyl-1-propyl acetate hydrochlorides was obtained. Moreover, in the method of preparation of the above-mentioned hydrochloride, L-lactic acid, a citric acid, or a succinic acid is used instead of a hydrochloric acid, and it is 1S and (2S)-2-decanoylamino-3-morpholino-1-phenyl-1-propyl. The salt of each above-mentioned carboxylic acid of acetate was prepared.

[0083] Example 2 () 1S, 2S-2-decanoylamino-3-morpholino-1-phenyl-1-propyl Composition -2 of N and N-dimethylamino acetate (1S, 2S) - 902.1mg of decanoylamino-3-morpholino-1-phenyl-1-propanol hydrochlorides (2.03mmol), dicyclohexylcarbodiimide 709.6mg (3.44mmol), 20ml of methylene chlorides was added to 216.2mg

[of N,N-dimethylglycine] (2.10mmol), N, and N-dimethylamino pyridine 98.5mg (0.806mmol), and it agitated for bottom two days of a room temperature. Filtration removal of the white crystal was carried out after reaction termination, chloroform 100ml was added after condensing a filtrate, sequential washing of the organic layer was carried out by the saturation sodium-hydrogencarbonate solution, water, and 70ml of each saturation brine, on the sodium sulfate, after desiccation, it filtered and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (ethyl acetate: methanol =9:1) refined the obtained rough product, and 713.8mg (74.1% of yield) of red oil-like mark matter was obtained.

TLC Rf.0.33 (chloroform: methanol =20:1), 0.19(ethyl acetate: methanol =9:1) 1 H-NMR (CDCl₃) : 7.34-7.26 (5H, m, aromatic), 6.13 (1H, d, J= 4.39Hz, H-1) 5.95 (1H, d, J= 8.79Hz, NH), 4.51 (1H, m, H-2) 3.65 (4H, m, 2(CH₂) O), 3.25 (2H, d, J= 2.93Hz, COCH₂N), 2.44 (4H, m, N(CH₂)₂) 2.35-2.32 (8H, m, H-3, N₂ (CH₃)), 2.11 (2H, m, COCH₂) 1.53 (2H, m, COCH₂CH₂), 1.25 (12H, m, 6(CH₂) CH₃), 0.88 (3H, t, CH₂CH₃) 13 C-NMR (CDCl₃) : 172.8, 169.5, 137.5, 128.4, 128.2, 126.5, 75.1, 67.0, 60.5, 59.2, and 53.8, 50.4, 45.3, 36.7, 31.8, 29.4, 29.3, 29.2, 25.7, 22.6, and 14.1 [0084 --] Example 3 () 1S, 2S-2-decanoylamino-3-morpholino-1-phenyl-1-propyl Composition -2 of methoxy acetate (1S, 2S) - 982.2mg (2.207mmol) of decanoylamino-3-morpholino-1-phenyl-1-propanol hydrochlorides Melt to 20ml of methylene chlorides, and bottom pyridine of room temperature 0.357ml (4.41mmol) and methoxy acetyl chloride 0.242ml (2.65mmol) are added and agitated. 24 hours after pyridine 0.179ml (2.207mmol) and methoxy acetyl chloride 0.202ml (2.207mmol) were added. After reaction termination and after adding methanol 5ml and agitating for 20 minutes, reduced pressure distilling off of the solvent is carried out, 100ml of ethyl acetate is added, and it is 1 N about an organic layer. Sequential washing was carried out by a hydrochloric acid, water, the saturation sodium-hydrogencarbonate solution, water, and 70ml of each saturation brine, on the sodium sulfate, after desiccation, it filtered and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (chloroform: methanol =40:1) refined the obtained rough product, and the 1,000.8 mg (98.2% of yield) colorless oil-like mark matter was obtained.

TLC Rf.0.39 (chloroform: methanol =20:1), 0.48 (ethyl acetate: methanol =20:1)

1 H-NMR (CDCl₃) : 7.36-7.27 (5H, m, aromatic), 6.14 (1H, d, J= 4.88Hz, H-1) 5.64 (1H, d, J= 9.28Hz, NH), 4.54 (1H, m, H-2) 4.09 (2H, m, CH₂OCH₃), 3.64 (4H, m, 2(CH₂) O) 3.44 (3H, s, OCH₃), 2.48-2.37 and 2.35-2.30 (6H, m, CH₂N₂ (CH₂)), 2.12 (2H, m, COCH₂) 1.54 (2H, m, COCH₂CH₂), 1.25 (12H, m, 6(CH₂) CH₃), 0.88 (3H, t, CH₂CH₃) 13 C-NMR (CDCl₃) : 172.8, 169.3, 137.1, 128.5, 128.4, 126.6, 75.5, 69.8, 66.9, 59.4, and 59.0, 53.8, 50.3, 36.8, 31.8, 29.4, 29.3, 29.2, 29.1, 25.7, 22.6, 14.0 [0085] Example 4 () 1S, 2S-2-decanoylamino-3-morpholino-1-phenyl-1-propyl Composition -2 of hydronium gene succinate (1S, 2S) - 950.6mg (2.136mmol) of decanoylamino-3-morpholino-1-phenyl-1-propanol hydrochlorides Melt to 220ml of methylene chlorides, and bottom pyridine of room temperature 0.346ml (4.272mmol) and 346.1mg (3.459mmol) of succinic anhydrides are added and agitated. 24 hours after pyridine 0.141ml (1.737mmol) and 173.8mg (1.737mmol) of succinic anhydrides were added. After reaction termination and 1 N After adding 70ml of hydrochloric acids and agitating for 20 minutes, it extracted by chloroform 100ml and sequential washing of the organic layer was carried out by water, the saturation sodium-hydrogencarbonate solution, water, and 70ml of each saturation brine, on the sodium sulfate, after desiccation, it filtered and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (chloroform: methanol =20:1) refined the obtained rough product, and 637.1mg (54.7% of yield) of white ****-like mark matter was obtained.

TLC Rf.0.24 (chloroform: methanol =9:1), 0.12(ethyl acetate: methanol =9:1) 1 H-NMR (CDCl₃) : 7.35-7.26 (5H, m, aromatic), 6.40 (1H, d, J= 9.27Hz, NH) 5.96 (1H, d, J= 4.39Hz, H-1), 4.63 (1H, m, H-2) 3.74-3.62 (4H, m, 2(CH₂) O), 2.82-2.57 and 2.39-2.35 (10H, m, COCH₂CH₂CO, CH₂N₂ (CH₂)), 2.14 (2H, m, COCH₂) 1.51 (2H, m, COCH₂CH₂), 1.25 (12H, m, 6(CH₂) CH₃), 0.88 (3H, t, CH₂CH₃) 13 C-NMR (CDCl₃) : 176.8, 173.5, 171.5, 137.0, 128.6, 128.4, 126.4, 75.3, 65.6, 58.3, and 53.0, 49.3, 36.5, 31.9, 30.4, 30.3, 29.5, 29.4, 29.3, 25.5, 22.6, 14.1 [0086] Example 5 () 1S, 2S-2-octyloxy carbonylamino-3-morpholino-1-phenyl-1-propyl Composition -2 of acetate (1S, 2S) - 1034.5 mg octyloxy carbonylamino-3-morpholino-1-phenyl-1-propanol Melt (2.639mmol) to 26ml of methylene chlorides, and bottom pyridine of room temperature 0.54ml (6.677mmol) and 0.5ml (5.304mmol) of acetic anhydrides are added and agitated. 14 hours after pyridine 0.54ml (6.677mmol) and 0.5ml (5.304mmol) of acetic anhydrides were added. After reaction termination and after adding methanol 5ml and agitating for 20 minutes, reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (n-hexane: ethyl-acetate =1:1) refined the obtained rough product, and 915.2mg (79.9% of yield) of colorless oil-like mark matter was obtained.

TLC Rf.0.44 (CHCl₃:MeOH=20:1), 0.21 (n-Hexane:AcOEt=1:2)

1H-NMR(CDCl₃): 7.35-7.26(5H, m, aromatic), 6.02(1H, d, J=3.91Hz, H-1), 4.83(1H, d, J=7.81Hz, NH), 4.13(1H,

m, H-2), 3.97(2H, m, COO-CH₂), 3.67(4H, m, (CH₂)₂O), 2.50-2.31(6H, m, CH₂N(CH₂)₂), 2.12(3H, s, COCH₃), 1.53(2H, m, COOCH₂CH₂), 1.27(10H, m, (CH₂)₅CH₃, 0.89 (3H, t, CH₂CH₃) 13 C-NMR(CDCl₃): 169.7, 156.4, 137.8, 128.4, 128.1, 126.5, 74.9, 67.0, 65.2, 59.6, and 53.9, 52.7, 31.8, 29.2, 29.0, 25.8, 22.6, 21.0, 14.0 [0087]

Example 6 () 1R, 2R-2-benzyloxycarbonylamino-3-pyrrolidino-1-phenyl-1-propyl Synthetic (R [1], 2R) -2-benzyloxycarbonylamino-1-phenyl-3-pyrrolidino-1-propanol 284.2mg of acetate (0.803mmol) was melted to pyridine 5ml, on the ice bath, 151.4micro (1.61mmol) of acetic anhydrides I was added, it agitated under the room temperature, and 38.0micro (0.403mmol) of acetic anhydrides I was added 16 hours after. It is 1 N after reaction termination. After adding 30ml of hydrochloric acids and agitating for 20 minutes, 50ml of ethyl acetate extracted, sequential washing of the organic layer was carried out by water, the saturation sodium-hydrogencarbonate solution, water, and 30ml of each saturation brine, on the sodium sulfate, after desiccation, it filtered and reduced pressure distilling off of the solvent was carried out. Moreover, the doubled washings was extracted 3 times by chloroform 70ml, the organic layer was filtered after desiccation on the sodium sulfate, and reduced pressure distilling off of the solvent was carried out. The obtained rough product was doubled, the silica gel column chromatography (chloroform: methanol =20:1, ethyl-acetate:methanol =20:1) refined, and 230.9mg (72.6% of yield) of colorless oil-like mark matter was obtained.

TLC Rf.0.24 (chloroform: methanol =20:1), 0.31(ethyl acetate: methanol =9:1) 1 H-NMR (CDCl₃) : 7.34-7.25 (10H, m, aromatic), 5.95 (1H, d, J= 4.88Hz, H-1) 5.10-4.94 (2H, m, COOCH₂), 4.17 (1H, m, H-2) 2.51 (6H, m, CH₂N₂ (CH₂)), 2.03 (3H, s, COCH₃), 1.73 (4H, m, and H-3', H-4') 13 C-NMR (CDCl₃) : 169.7, 156.1, 137.7, 136.6, 128.6, 128.3, 128.2, 128.0, and 127.9, 126. A hydrochloride can be similarly prepared by the approach which also showed the compound of 6, 75.3, 66.5, 56.5, 54.5, 54.3, 23.5, and 20.8 examples 2-6 to the example 1. [0088] examples 7-10 -- the ester corresponding to each raw material can be obtained by using for a raw material the compound shown in the examples 7-10 of preparation again, and esterifying a hydroxyl group by the same approach fundamentally using each carboxylic acid shown in examples 1-4, or its reactant derivative.

[0089] Example 11 The improvement effect [experiment approach] animal of L-threo-PDMP to the space perception memory disorder of a repeat brain ischemia rat and L-threo-PDMP acetate trained the 8 direction radial maze technical problem once per day, and made space perception gain using a Wister system male rat (weight: 250-280g). According to Pulsinelli and Brierly's and others approach (Stroke, 10, 267, 1979), the cauterization of a vertebral artery and the ablative operation of a common carotid artery were performed to the rat which gained space perception, and ischemia treatment was performed only using the rat which has checked that an operation did not have effect in execution of a maze technical problem on the next day [the]. Ischemia treatment ligated the common carotid artery using the clip for 10 minutes under no anesthetizing, ligated it for 10 more minutes 1 hour after the blood-flow restart, and performed 2 times of repeat ischemia. Playback trial was performed after one week of ischemia treatment, and results were expressed as the number of forward selections of the first eight selections, and the number of false drops in the observation time amount for a maximum of 10 minutes (refer to drawing 1). moreover, the effectiveness of a drug -- extent of an improvement -- higher efficacy (7 or more and the number of false drops show [the number of forward selections] one or less) -- it evaluated to the three-stage of effective (7 or more and the number of false drops show [the number of forward selections] 2 or 3), and an invalid (the number of false drops shows four or more), and expressed as the rate of an improvement (refer to drawing 2).

[0090] [Result] Comparison examination of the effectiveness of L-threo-PDMP and L-threo-PDMP acetate that the ganglioside biosynthesis facilitatory effect is checked was carried out to the space perception memory disorder after one week of repeat brain ischemia in the 8 direction radial maze technical problem using a rat. specifically, both compounds are dissolved in a Tween 80 content physiological saline 1.5% -- making -- 2 mg/kg (i. v.) the bis die from 24 hours after ischemia treatment -- repetitive administration was carried out for six days.

[0091] The number of forward selections about each trial group and the number of false drops are shown in drawing 1 . consequently, as for the repetitive administration group during six days of both compounds, the increment in the significant number of forward selections and reduction of the significant number of false drops were accepted to the control group (a 1.5%Tween 80 content physiological saline -- administration; -- it expresses ischemia among drawing 1). That is, in the space perception memory disorder model by repeat brain ischemia, it turned out that it becomes clear that an improvement operation is shown and it is expected as a cerebrovascular-disease sequela remedy with very high clinical value also by the administration from after [the ischemia] 24 hours which the nerve cell failure of an acute stage has already produced. Moreover, it became clear that L-threo-PDMP acetate was superior to L-threo-PDMP in both reduction of the increment in the number of forward selections and the number of false drops, and the usefulness of L-threo-PDMP acetate was proved. In addition, the inside sham of drawing 1 expresses the rat to which an operation did not perform ischemia treatment among the rats which have

checked that there was no effect in execution of a maze technical problem on the next day which performed the cautery of a vertebral artery, and the ablative operation of a common carotid artery.

[0092] Moreover, the results of each medication were shown in drawing 2 as a rate of an improvement in individual level (4 or more [7 or more two false drops or 3, an invalid: Higher efficacy: The number of forward selections 7 or more, the number of false drops effective / one or less / : the number of forward selections the number of false drops]). Consequently, it became clear that L-threo-PDMP acetate has the high ratio of higher efficacy as compared with L-threo-PDMP. In addition, among drawing 1 and 2, L-threo-PDMP was abbreviated to L-PDMP and indicated.

[0093] Example 12 After taking out an embryo from the Wister system rat (Japan SLC) on neural spine expanding activity [experiment approach] pregnancy the 17th of L-threo-PDMP and L-threo-PDMP acetate in sterile (eight embryos), the brain was taken out from the embryo, the cerebellum was removed under the stereoscopic microscope, and the midbrain was removed from the cerebrum. Furthermore, meninges were stripped off from the cerebral cortex and it was made only the cerebral cortex. The fragment of the cerebral cortex for eight animals was respectively carried out 100 times in all directions with the injector razor on 60mm pan, and 5ml phosphate buffered saline (PBS) was added twice, the explant (Explant) was washed from the pan, and it carried out centrifugal [for 500rpm x 1 minute]. A pellet is made to add and suspend DMEM(Dulbecco's modified Eagle's medium)4ml except for the supernatant liquid containing a single cell (single cell), and it pours distributively in every 50ml 1ml falcon tube, and is DMEM. 12ml was added. The tube was bound around four 24 hole plates (2cm²) which carried out the coat by polyethyleneimine 0.1% in the condition of having made it suspending with a swing (1.66x105cells/500microl/well).

[0094] 2 hours after culture -- supernatant liquid 50microl Compound A (L-threo-PDMP acetate) 50microl which was sampled and was compounded in the example 1-1 and the compound B compounded in the example 5 -- final concentration 5-20microM It added so that it might become. It is 500microl about 1% glutaraldehyde after cultivating for two days / PBS. In addition, it fixed for 20 minutes at the room temperature. Immediately after removing supernatant liquid in the suction, multistory [of the 0.5mlPBS] was carried out slowly, and it removed in the suction. Multistory [of 20% Giemsa's solution / the potassium phosphate buffer solution (after setting 6.63g of potassium dihydrogenphosphates and 2.56g of disodium hydrogenphosphate to 1,000ml with distilled water and checking that it is pH6.4 with the pH indicator paper, it was used having diluted 10 times)] was carried out slowly, and it was placed at the room temperature for 2 hours. 5% methanol / PBS after removing supernatant liquid in a suction Multistory [of the 1.0ml] was carried out slowly, and it bleached at the room temperature for 20 minutes. PBS after removing supernatant liquid in a suction 0.5ml was added. At x40-x100 time, it is 50-200 micrometers under a microscope. Extent of neural spine expansion of Explant was measured 100 or more groups. Evaluation is each. It has a neural spine longer than the diameter of Explant. The number of Explant(s) was written by abundance, having used control (additive-free) as 100%.

[0095] [Result] The neural spine expanding activity (%) in compound A and the maximum effective concentration (both 10microM) of B was shown in drawing 3 . The neural spine expanding promotion activity in in vitro of L-threo-PDMP acetate became clear from this result.

[0096] Example 13 In order to check the brain protective action of the prolongation-of-life effectiveness this invention compound of the L-threo-PDMP acetate to a potassium-cyanide inducement hypoxia (KCN Hypoxia) mouse model, The 1.5%Tween 80 content physiological saline solution of L-threo-PDMP acetate These compounds 2 and 8 and 20 mg/kg A medicine is prescribed for the patient into the vein of a mouse (n= 5) by each dosage, and it is potassium-cyanide (KCN) 2.4 mg/kg the 1 hour after further. A medicine was prescribed for the patient into the vein, and the survival rate of 1 hour after was examined.

[0097] Consequently, control group (only KCN administration, n= 5) They are 8 and 20 mg/kg to being 5% of survival rate (LD95). this invention compound administration group showed 80% of survival rate. Moreover, 2 mg/kg this invention compound administration group showed 40% of survival rate.

[0098] It thought based on the brain protective action of this invention compound, and the usefulness as a brain protective agent of this invention compound was shown by the above result.

[0099] In addition, in each above-mentioned dosage, the effect of this invention compound to the blood pressure and the heart rate to a SHR rat and a normal rat was not accepted.

[Translation done.]

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TECHNICAL FIELD

[Field of the Invention] This invention relates to the physic containing the amino alcohol derivative and it which are a ceramide analog, especially the therapy agent of a nervous disease.

[Translation done.]

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PRIOR ART

[Description of the Prior Art] Sphingoglycolipid (henceforth GSL) exists as a cell membrane surface constituent of a mammalian cell, and it is known that it is closely related to cell functions, such as generating through the receptor function of a physiological active substance, the mutual recognizing ability between cells, or biotaxis, growth, differentiation, canceration, and an immunoreaction.

[0003] Especially, ganglioside is GSL containing a sialic acid and the effectiveness of the exogenous ganglioside to the various symptoms models of a nervous system is examined by recovery of nervous diseases, such as peripheral nerve injury and a central-nerves failure, i.e., the flume crack which has activity in the nervous promotion of playback and a nervous neural transmission process, and current. It is already KURONA sial (CronassialTM) in Italy as drugs using this. Kamiichi of the drugs is carried out and related patent application is made (JP,52-34912,A).

[0004] Although current and the thing currently that as the technique of exploring the function of ganglioside used are things of the type of adding ganglioside from outside in an experiment system, relation with endogenous ganglioside poses a problem in that case. [most] That is, it is thought that the result from which the endogenous ganglioside which exists in a cell membrane adds ganglioside further in [which have already formed complex] various cell surface receptors etc., and is drawn in is not always reflecting a true cell physiology-meaning of endogenous ganglioside. therefore -- in order to know the original role on the cell physiology of ganglioside -- endogenous -- the method of changing the biosynthesis of GSL specifically was required. this invention person etc. is 1-phenyl-2-decanoylamino-3-morpholino-1-propanol which is the analog of ceramide previously. (PDMP) It compounds. all the cells of GSL to which D-threo-PDMP checks a glucoseylceramide biosynthesis enzyme specifically, and uses a glucoseylceramide as starting material -- entailment -- it proved decreasing an amount remarkably (J.Lipid.Res., vol.28, 565-571, 1987).

[0005] Furthermore, a GSL content falls by D-threo-PDMP and it is reported that expansion of a neural spine is controlled by this (103 J. Biochem., 110, 96- 1991). Moreover, D-threo-PDMP controls a synapse function and it is found out that this control is specifically canceled by GQ1b in various gangliosides

(Biochem.Biophys.Res.Commun., 222, 494-498, 1996). From this result, the importance which it is suggested that ganglioside GQ1b is an activated molecule indispensable to a synapse function, and it exerts on the neurological function of endogenous ganglioside is recognized.

[0006] this invention persons have found out that L-threo-PDMP which is the optical antipode of D-threo-PDMP may promote the biosynthesis of GSL on the other hand (J.Cell.Physiol., 141, 573-583 (1989)). However, [whether L-threo-PDMP makes the endogenous ganglioside level of a nerve cell increase, and whether the increment in endogenous ganglioside activates the function of a nerve cell again], it is a strange problem and examination was not made at all.

[0007] Then, by promoting the ganglioside biosynthesis of a nerve cell, 2-acylamino propanol derivatives, such as L-threo-PDMP, demonstrated the neural spine expansion facilitatory effect (J.Neurochem., 67, 1821-1830 (1996)) and the synaptogenesis facilitatory effect, and, as for this invention persons, have found out that it is promising as a neurotropia agent (PCT international public presentation WO 95/05177).

[0008] The recently and this invention persons are MAP activated when synaptic transmission is continuously risen by N-methyl-D-aspartate (NMDA), a brain-derived neurotrophic factor (Brain Derived Neurotrophic Factor; BDNF), etc. for the purpose of the elucidation of the action mechanism of the neurotrophic factor Mr. activity of L-threo-PDMP. The effect of this matter to a kinase (MAPkinase; mitogen-activatedprotein kinase) was considered. Consequently, L-threo-PDMP is proportional to a synaptogenesis facilitatory effect, and MAP. It has become clear that long duration activation of the kinase is carried out. Furthermore, the activation effectiveness of the GQ1b

synthetic enzyme activity by L-threo-PDMP is also found out.

[0009] However, above L-threo-PDMP is in vivo. When demonstrating drug effect, it was judged that there was room of amelioration further about the half-life in blood and brain internal transmigration nature.

[Translation done.]

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TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] this invention persons found out that solubility was improved remarkably by esterifying the hydroxyl group of 2-acylamino propanol derivatives, such as L-threo-PDMP. Moreover, when mammalian was medicated with esterified L-threo-PDMP, it checked having the neuriatric effectiveness and the brain protective action superior to L-threo-PDMP. Based on these knowledge, it came to complete this invention.

[Translation done.]

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DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1] The effectiveness exerted on the number of forward selections and the number of false drops of L-threo-PDMP to the space perception failure of a repeat brain ischemia rat and L-threo-PDMP acetate is expressed.

[Drawing 2] The space perception memory disorder improvement effect in the individual level after L-threo-PDMP acetate and L-threo-PDMP repetitive administration is expressed.

[Drawing 3] Compound compounded in L-threo-PDMP acetate (compound A) and the example 5 (compound B) Neural spine expanding activity is expressed.

[Translation done.]

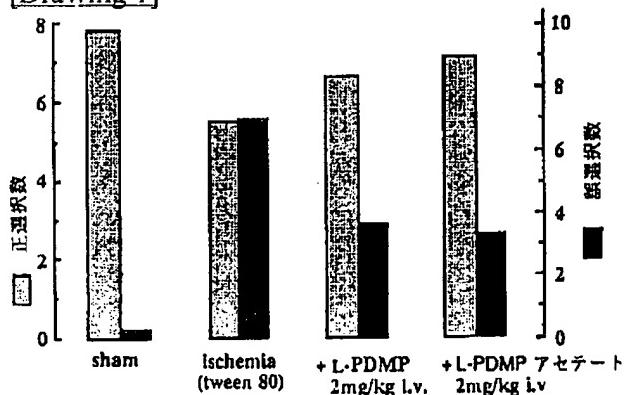
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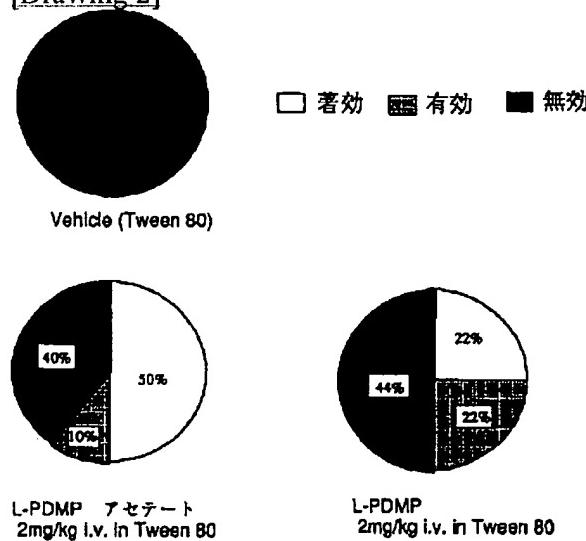
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DRAWINGS

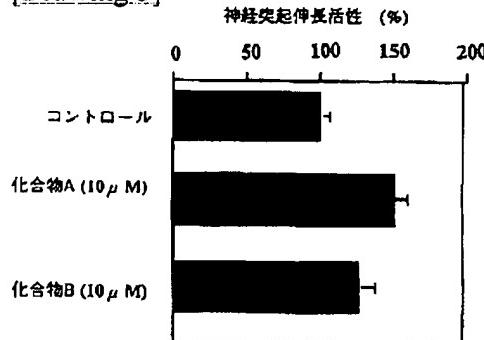
[Drawing 1]



[Drawing 2]



[Drawing 3]



[Translation done.]